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# BULLETIN OF THE NEW YORK ACADEMY OF MEDICINE

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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

AUGUST, 1942

# NUTRITION AND THE NATION AT WAR*

JAMES S. MCLESTER

Professor of Medicine, University of Alabama

IN the war of today everybody fights. True, only a limited section of the population, the soldiers, the sailors, and the aviators, take part in the actual shooting, but all—men and women alike—are subject to the stress and strain and the anxieties and dangers of war; all must work toward ultimate success. The Central Empires were defeated in the last great war because the population behind the lines lost their morale and caved in. France today is a conquered nation, not because her armies were defeated in battle but because morale was at such a low ebb that, at the enemy's first onslaught, all resistance collapsed. To wage successful war it is necessary not only that a nation possess armed forces of surpassing valor, adequately equipped, but also that it have an industrially efficient citizenry of inflexible stamina. Both are essential.

These two qualities, efficiency and stamina, depend upon many factors: inheritance, training, education, and—to an enormous degree—nutrition. It is a common saying that "The poorly fed soldier isn't worth a damn." Within limits, the same can be said of the poorly fed civilian, for such persons are as a rule timid, anxious, nervously un-

* The Hermann M. Biggs Lecture, given April 2, 1942 at The New York Academy of Medicine.

stable, and lacking in efficiency. It is among these that fifth columnists find their most fertile field. This nation cannot, therefore, content itself merely with drafting its youth into its armies, training them, and providing them with ammunition and equipment. It must do more. It must see to it first, that the armed forces are adequately supplied with good food and second, that the general population also is well-nourished.

The first of these objectives, the feeding of the army, is not difficult. The Medical Department and the Subsistence Division of the Quartermaster's Department of the United States Army are thoroughly enlightened as to the nutritive needs of the soldier and have adequate funds with which to purchase the best possible rations. The same can be said of the navy.

There are, however, certain special problems, technical in nature, upon which expert advice is sought; and to furnish this is one of the functions of the National Research Council. At the request of the Surgeons General, this Council has organized several committees, and subcommittees, one of which is the Subcommittee on Medical Nutrition. This Subcommittee consists of six physicians and one biochemist all of whom are especially interested in nutrition; three of them are members of the Council on Foods and Nutrition of the American Medical Association. With this group also sit representatives from the Army, Navy, and Public Health Service. Its discussions include everything that has a bearing on the nutrition of the armed forces. It has studied in detail the garrison ration and the field ration and has spent a great deal of time discussing the food to be used under special conditions, notably that required by parachute and mobile troops and by troops serving under extremes of temperature such as are found in the Tropics and in Alaska.

The garrison ration requires little discussion. It includes almost everything of value which the market affords; is abundant in amount and provides liberal quantities of minerals, vitamins, and good protein. In quality and balance it leaves nothing to be desired.

One of the difficulties encountered has been the determination, not merely of what food is to be provided the soldier, but, equally important, of what part of this he actually utilizes. This will be answered, it is hoped, by certain forms recently devised by Colonel Paul Howe of the Surgeon General's Office, which not only record the food provided, but also that not eaten or otherwise wasted. The Subcommittee has been

interested, too, in other less obvious forms of wastage notably the losses which occur in the processing of food and in its preparation for the table. This last question will be referred to again.

The field ration has been more difficult to arrange because of the necessity for compactness and stability. That now in use consists of previously cooked or prepared food, packed in hermetically sealed cans. It may be eaten either hot or cold. Each ration, that is, the food for one soldier for one day, consists of six cans; three of these contain a meat and vegetable stew or hash and three contain crackers, sugar and soluble coffee. This ration is palatable; is adequate nutritionally; and in other respects also appears to be entirely suitable.

In this day of mechanized warfare, however, when the soldier must cover long distances in a few hours, even the field rations cannot be expected always to keep up with him and many troops, notably the parachutists, must carry on their person food which will sustain them in fighting trim for several days. The difficulties encountered in devising such rations are manifold. The food must be palatable and nutritionally adequate; it must have no thirst-provoking or other undesirable qualities; and it must be compact and stable. It was at first thought that the chocolate bar, appropriately reinforced with yeast and vitamins, would meet these specifications, for it has great nutritive value, is stable and can be made into a compact form eminently suitable as an emergency ration. Experience has shown, however, that chocolate has definite disadvantages, particularly in its tendency to produce thirst, gastrointestinal disorders and headache. For this reason chocolate has been discarded as the basis of the ration and is now used only as a supplement. Colonels Isker and Logan and their associates in the Subsistence Division of the Quartermaster's Department have shown great ingenuity and skill in devising a ration which consists of several components packed in a conveniently carried container, and this is now being thoroughly tested under campaign conditions. To the subcommittee this ration seems well adapted to the purposes for which it is designed.

The administration of multiple vitamins to the armed forces has been discussed at length. A difficulty was at first encountered in the fundamental opposition of the Council on Pharmacy and Chemistry of the American Medical Association to all forms of polypharmacy, including the administration of polyvitamin preparations. Indeed, this Council and the Council on Foods and Nutrition have always deplored the wide-

spread and indiscriminate consumption by the public of the many vitamin preparations of varying composition and uncertain potency now on the market. It was decided, however, about a year ago at a joint meeting of these two Councils to reëxamine the entire problem of vitamin therapy, and in recognition of the multiple nature of almost all deficiency disorders seen in America, it was decided to reverse this policy in respect to vitamins. Multiple vitamin preparations are now accepted provided these substances are included in definitely specified amounts. Following this action by the two Councils of the American Medical Association, the Subcommittee on Medical Nutrition of the National Research Council recommended the use by the Army and Navy of capsules or tablets containing vitamins in appropriate amounts to be administered when needed one to three times daily as directed by the Medical Corps.

It was subsequently recommended that for use under conditions of temporary nature 400 I.U. of vitamin D also be included.

In considering this use of vitamins the Subcommittee has been very much interested in the endurance experiments conducted by Ancel Keyes of the University of Minnesota. Keyes completed a four months' study on thirty track men and on three groups of soldiers, each studied over a period of twelve weeks, and concluded that "Vitamin Super Charging" of properly nourished men has no beneficial effect on the performance of muscular work or on recovery from that work. This applies whether the work period be brief, intense, or prolonged. It seems fair to conclude from his work that the administration of vitamins to the well-nourished soldier can add nothing to his endurance or to his fighting qualities. The important thing is to provide him under all conditions with the optimum ration.

In many other respects also the nutritive needs of the armed forces are being considered. The advisability, for example, has been considered of giving additional vitamin A to those whose acuteness of vision in semi-darkness is of vital importance. Also, in view of the extremes of temperature under which the soldier and sailor must sometimes work and fight, considerable thought has been given to the prevention of heat exhaustion. On the advice of J. H. Talbott, the Subcommittee has recommended under conditions of high temperature and great humidity the use of salt tablets or, still better, the addition of 0.1 per cent sodium chloride to all drinking water. At present the tablets are being used. The Subcommittee has not neglected to examine the rations

issued troops of other nations, and it is proper to add that no brilliant innovation, as was once predicated, has been found. It is not possible to go into further detail regarding the nutrition of the Armed Forces of this Country, but I can tell you that the food of the American soldier and sailor is well-balanced, is suited to his needs and is the best obtainable. I think it safe to say, too, that no other soldier or sailor has ever been as well fed.

Turning to the second objective, adequate food for the entire Nation, one can properly ask: Is there need for improvement in the average American diet? Is nutritive failure a retarding factor in the lives of the American people? I would unhesitatingly answer "yes," but there are many physicians of experience who answer "no." I doubt, however, if these physicians are looking at the whole picture. True, frank outspoken deficiency disease is relatively rare in America, at least it seldom stares one in the face, but this is not the type of deficiency to which reference is made. It is the borderline state of nutritive failure, a state in which the patient is neither sick nor entirely well, that holds greatest interest. This often expresses itself merely in nervousness, lowered morale, and lack of efficiency. Evidence that these symptoms are frequent manifestations of low grade nutritive failure is accumulating. It has been found in Birmingham, for example, that the case histories of many pellagrins reveal that in the previous year, before clearly recognizable disease appeared, these patients had been admitted to the hospital as neurasthenics. They were vaguely sick before they had frank pellagra. Witness the carefully controlled studies of Wilder and his associates in Minnesota who found that the withdrawal of thiamine from the diet of a group of persons produced within a short time nervousness, listlessness, and mental depression, which symptoms promptly disappeared when the missing substance was restored, and the observations of like nature made by Jolliffe in New York. From Toronto comes the report of Ebbs, Tisdall, Scott and their co-workers who added supplements to the diets of a group of ninety pregnant women and found that the subsequent course of pregnancy, labor and the puerperium was vastly better in these subjects than in the controls. These women were not sick, but evidently they were sorely in need of the additional food given them. They were of that group of persons who live in the twilight zone of nutrition. Though perhaps lacking in vigor and efficiency, such persons present no clear evidences of nutritive deficiency and manage

to maintain a semblance of health. Subject them, however, to some physiologic strain, a febrile illness, hyperthyroidism, pregnancy, a period of unusual physical exertion, an attack of diarrhea, an operation, or perhaps mere curtailment in food intake, then nutritive failure is precipitated and evidences of ill-health appear. Pertinent to this discussion also is the experience of students of nutrition who find that rats and other experimental animals when undernourished even in small degree become irritable and difficult to handle and that when the lacking substance is supplied the animals become as a rule sleek, docile and easy to handle. For a more complete answer to this question the reader is referred to the recent review by Jolliffe, McLester and Sherman.

It is unfortunate that few methods of precision are available by which lack of vitamins can accurately be gauged. The dark adaptation test for detecting vitamin A deficiency and the use of the slit lamp for revealing the small vessels in the cornea which tell of riboflavin deficiency are of promise, but the only chemical methods which are clinically available are those which tell of the plasma proteins and of the ascorbic acid and vitamin K in the blood. No doubt, other methods of analysis will soon be available, but there will still remain certain fundamental difficulties which must be reckoned with, notably the fact that the figures which tell of the amount of a vitamin in the blood do not necessarily reveal the supply of that substance held in the tissues; and it is this last which tells the story. The most readily available testimony as to nutritive deficiency today, therefore, can be found in a host of clinical signs, notable among which are the personality changes just mentioned, and certain characteristic physical signs. Among these last are changes in the color and texture of the tongue, often with papillary atrophy, tell-tale cracks at the corners of the mouth and nose, typical changes in the sclera, vascularization of cornea, easy fatiguability coupled with tenderness in the calf muscles, cryptic hemorrhages, especially of the gums or into the skin or joints, unexplained edema, and certain types of diarrhea. To the initiated these signs point to nutritive failure. They are not rare. A list of these symptoms and signs was compiled for the Subcommittee on Medical Nutrition of the National Research Council by a subgroup under the chairmanship of Thomas Mackie and was published in a recent issue of the Journal of the American Medical Association. Reprints may be secured from the Nutrition Division, Office of Defense Health and Welfare Service, Washington, D. C.

The American people are not starving, far from it, but there is ample reason for the belief that general improvement in the diet, particularly in respect to vitamins and minerals, will result in a higher degree of emotional stability and greater vigor. This will in turn increase the efficiency of the American workman in the defense industries and will add to the stability of the citizen in his determination to win the war.

The accomplishment of this, however, is not simple; many factors are concerned. First among these is adequacy of supply. This problem of producing the food and getting it to the people belongs to agriculture, commerce, and transportation, all of which in the last analysis is the concern of government. Only gradually are governments coming to realize that it is not alone the total amount of available food which counts; but, equally important, the quality and kind. Measures must be taken to supply the protective foods especially, milk, butter, eggs, fruits, and green vegetables, and so to regulate commerce and transportation as to favor their easy exchange. In addition, in order to insure the preservation of the contained vitamins the proper handling and refrigeration of fruits and vegetables should be facilitated. Dried foods, for example, offer a possible solution of many of these problems, but in the present state of the industry these foods are not often dependable. Properly dehydrated fruits and vegetables retain all of their nutritive essentials in good measure, but examination of the produce on the market today indicates that the processing is seldom carried out efficiently and that the products, as purchased, are often grievously lacking in essential nutrients. This has been of concern to both the Subcommittee on Medical Nutrition and to the Food and Nutrition Board of the National Research Council, for the use of desiccated vegetables and fruits would obviate many difficulties of storage and transportation. In the present status of this industry, therefore, it is not possible for the Army and Navy to make general use of dried vegetables or for physicians to recommend these to the public. Improvement will, no doubt, come through the encouragement of the industry and the standardization of its methods. All of this will require policies in agriculture, manufacture, and commerce which have not yet been formulated but which in the distance are dimly discernible.

Supply, however, is not the only problem. The people must be induced to eat what they need, and this is a matter of education. Even the economic problem can in part be solved by education, for with

proper guidance the housewife can learn to make a highly restricted budget stretch a long way in the purchase of nutritious foods. The most expensive articles are not necessarily the most nutritious. Large red apples, the best cuts of meat, and neatly packaged breakfast foods are not bargains in food value. The housewife should know this and should learn that there is ample room for discrimination in buying the family's food. Fads, fancies, tabus, and customs, both familial and racial, as well as gross ignorance, must all be overcome. Such a program demands the participation of all responsible agencies, schools, universities, and health organizations, and, most important perhaps, it demands the sympathy and active encouragement of the medical profession.

The importance of such an educational program was clearly seen by the President when a year ago he called the National Nutrition Conference for Defense. The membership included physicians, biologists, chemists, nutritionists, economists, public health officers, nurses, labor leaders, and others. All shades of opinion were represented and from the deliberations of this conference came a number of recommendations. Among these were provisions for vigorous and continuous research in the field of nutrition, for the increased production of foods needed in greater abundance in the American diet, for improvement in food distribution, including processing, marketing and packing, and for the mobilization of all neighborhood, community, and state organizations that can contribute in any way to raising the nutritional level of the American people. Finally, the important suggestion was made that medical schools devote a greater part of their time to the teaching of nutrition.

The work of this conference is being implemented and extended by a smaller group, the Food and Nutrition Board of the National Research Council, headed at first by Russell Wilder, now by F. G. Boudreau. The function of this board is to study the nutritive status of the American people and to devise means by which this can, where needed, be improved. The thirty-three members were chosen from among the leading exponents of the science of nutrition. The membership includes ten physicians, five physiologists, eight chemists, six nutritionists, and two representatives each of Agriculture and food technology. Six of its members are members also of the Council on Foods and Nutrition of the American Medical Association.

This Board has already made important recommendations. The most

significant perhaps of the things accomplished is the improvement in the nutritive value of white flour. Milling processes will no doubt ultimately be developed to the point that those vitamins and minerals which are now lost in manufacture can be retained in the finished product, but at the present time it is desirable that the nutritive value of the flour, as now milled, be improved by adding these essential substances in pure form. In this process thiamine, nicotinic acid, or nicotinic amide and iron are being added in such amounts as to approximate the levels of whole wheat flour, that is, thiamine 1.66 mg., nicotinic acid or amide 6.15 mg. and iron, 6.15 mg. to the pound. Riboflavin is provided by the milk used in the final making of the bread. To this has been given the name "enriched flour" and to the bread a similar designation. Both are now to be found in grocery stores and bakeries. Whole wheat will not serve the same purpose. Its poor keeping qualities and the irritation it causes the intestinal tracts of susceptible persons offer distinct disadvantages. I am told that in England today no bread is permitted on the market except that which contains the essential ingredients just mentioned. It is hoped that in this country, also, enriched bread will soon take the place of the untreated white product. This Board has also standardized the addition of iodine to table salt (0.01 per cent of potassium iodide) and, in view of the increasing incidence of endemic goiter, is recommending the more general use of this product. It also advises the general fortification of oleomargarine with Vitamin A to the level of 9000 International Units per pound, and recommends that the use of oleomargarine be restricted to products which have been so fortified. If these amendments to the American diet are generally adopted then widespread improvement in nutrition may be expected.

Much of the work of this Board is done by its committees. One of these, under the chairmanship of Lydia Roberts, has compiled a much needed table of recommended daily allowances. You may ask why, with the abundant literature available, such a table is needed. Much of what is found in the literature is incomplete and contradictory, and it has seemed wise, as this committee has done, to put together in one statement the opinion of a number of experts. It is recognized that these figures are subject to revision, but they can be regarded as expressing well considered present-day opinion. This report, popularly known as the "yard stick," has been published by the Nutrition Division of the Federal Security Agency and is now being widely used as a guide for constructing

diets and for measuring the adequacy of current nutrition programs.

Since it is known that the efficiency of the worker is dependent to an enormous degree upon the adequacy of his diet there has been formed under the leadership of F. G. Boudreau a committee on industrial hygiene which is now studying the nutrition of the workers in a number of industrial plants of widely scattered areas. Abundant opportunity for improvement is seen. This is true even in many of the plants that undertake to provide lunches, for only too often little attention is paid to the nutritive adequacy of the food offered. Examination by a competent nutritionist, for example, of 700 lunch trays passing through the cafeteria line of a large plant, revealed that less than half of these could be classed as adequate. Through the efforts of this committee and that of other interested agencies it is believed that many of these faults will soon be corrected. I am told that every industrial plant of a certain size in Great Britain is required by law to furnish nourishing lunches and that the same is required of all schools. Indeed, information reaching this Country would indicate that, in spite of rationing and other restrictions, the nutritive status of the English worker is now on a higher level than before the war.

In this Country, also, employers of labor are fully aware of their responsibility in this respect. This is evidenced, for example, by the many inquiries that are being made concerning the advisability of administering polyvitamin capsules to all workers. To consider this rather insistent question a joint committee was formed from the Council on Industrial Hygiene and the Council on Foods and Nutrition of the American Medical Association. The answer given by this Committee, in brief, was definitely "No." It was recommended that vitamins in pharmaceutical form, essential as they often are, not be given indiscriminately, but that they be administered only for reason and under the advice of the physician. In short, the Council on Foods and Nutrition of the American Medical Association believes that the worker, like every other presumably robust person, should secure his vitamins and minerals, not from the pharmacist, but from the grocer and the dairyman.

I should like briefly to tell you more of the objectives of this Council for it contributes materially to the work I have attempted to describe. Originally, the Council on Foods and Nutrition of the American Medical Association was interested largely in promoting accuracy in labeling and truthfulness in advertising to the end that the American housewife,

when she buys her food, will know just what she is purchasing. Its efforts in this direction continue, but because of the breadth of the field it has been necessary in recent years to limit its consideration of specific articles largely to infant foods, special purpose foods and foods that have been nutritionally improved by various means. In another direction, however, the Council has greatly extended its scope and has assumed the more far-reaching function of promoting a broader, more wide-spread understanding of nutrition. Its activities in this direction include the preparation of informative reports, the sponsorship of reviews, and the encouragement of research. In these reports it endeavors to correlate and make readily available to the physician the new discoveries which are constantly being made in this extremely fertile field. This function of the Council will be well illustrated in the series of articles now being prepared under its auspices and soon to be published serially in the Journal. These articles, written by leading experts, will deal with all of the live problems of nutrition and can be regarded as authoritative. They will weigh recent discoveries critically, correlate them, examine them in their relation to medical practice and human welfare and in the light of the information thus gained, revise present-day knowledge.

We are engaged in a war that may be long and exhausting. It will be won or lost in this Nation's industrial plants. If we are to put in the field and on the seas armed forces of vigor and stamina; if we are to provide these forces adequately with armament, ships and air planes; if we are to give effective aid to our gallant allies; and if in the end we are to emerge victorious, then there are many things that must be done. Not the least important among these is the elevation of the nutritive status of the American people.

# THE PROPHYLACTIC TREATMENT OF RHEUMATIC FEVER BY SULFANILAMIDE

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RHEUMATIC fever is generally recognized as an acute disease with a great variety of clinical manifestations, which frequently recurs again and again in the same patient and may result in permanent organic heart disease. While rheumatic fever presents the clinical picture of an infectious disease, no bacteriological organism or virus has yet been consistently cultivated from the acute lesions, nor has the causative agent been directly established by other means. However, in the past ten or fifteen years a great deal of evidence has accumulated to show that acute attacks of rheumatic fever are usually preceded by some infection with the beta hemolytic streptococcus, such as acute pharyngitis or tonsillitis, or scarlet fever. Such an infection is usually followed by a latent period of one, two, or three weeks before the rheumatic episode begins. During the attack of rheumatic fever the antistreptolysin titer of the blood rises, even though the hemolytic streptococcus can no longer be cultivated from the throat of the patient, and this fact, also, has been considered to show some specific relationship between the antecedent beta hemolytic streptococcal infection and the period of rheumatic activity.

At present, there is no known specific cure for rheumatic fever. None of the sulfonamide drugs thus far developed have appeared to be of any value in combatting the acute attack of rheumatic fever, in contrast to their usefulness in lobar pneumonia, for example. The conservative measures of administering salicylates and keeping the patient at rest have only limited usefulness; they do not prevent renewed attacks of rheumatic fever, and they do not prevent the development of heart disease.

Since the first attack of acute rheumatic fever is seldom fatal, and rarely damages the heart severely enough to permanently impair its normal function, it seemed to me that the most important thing to be

done if possible was to prevent subsequent recurrences, once rheumatic fever had proclaimed itself, by preventing the antecedent beta hemolytic streptococcal infections. In 1935 and 1936 reports were published abroad concerning the protective effect of sulfanilamide in experimentally induced beta hemolytic streptococcus infections in mice. When the drug was administered before the streptococcus had had an opportunity to invade and multiply in the tissues, doses very much smaller than the usual curative dose proved effective prophylactically. These experiments made it seem worth while to undertake a carefully controlled study of the effect of administering small daily doses of sulfanilamide to patients recently recovered from acute rheumatic fever. By giving such prophylactic doses continuously over a long period of time we hoped that acute hemolytic streptococcal infections could be prevented in these rheumatic subjects, and that recrudescences of rheumatic fever would therefore not occur.

We embarked upon such a study in September 1936; the details of our observations during the first four years have already been published.[1, 2] In brief, we selected to receive the prophylactic treatment a group of adolescents and young adults, each of whom had had acute rheumatic fever within three years of entering the study, and observed other patients with similar histories as a control group. The patients were all ambulatory and in the quiescent phase of their disease; they were carefully followed in the Cardiac Clinic of the Department of Medicine in the Johns Hopkins Hospital. All had had one or more attacks of polyarthritis or carditis or both. The patients varied in age from seven to thirty-seven years, the great majority being between fourteen and twenty-six years of age. Sixty-nine per cent had chronic rheumatic endocarditis, 33 per cent had definite cardiac enlargement, but very few had definite reduction of the functional cardiac capacity. The treated and control groups were matched as closely as possible as to age, sex, race, history of rheumatic fever, and cardiac lesions.

The treated group were given sulfanilamide daily from October or November until June. The first year we gave 1 gram, or 15 grains a day in three 5 grain doses. The results that year were entirely satisfactory, but because we believed it was difficult for young people away from home, at school or at work, to remember to take the noon dose, the next year we altered the schedule to two 10 grain doses taken morning

TABLE I

COMPARISON OF THE INCIDENCE OF POSITIVE PHARYNGEAL CULTURES IN THE TREATED AND CONTROL GROUPS

| Season | *Treated Group During Sulfanilamide Season* | | | *Control Group During Control Season* | | |
|---|---|---|---|---|---|---|
| | *Total Number of Throat Cultures* | *Throat Cultures Positive for Beta Hemolytic Streptococci* | | *Total Number of Throat Cultures* | *Throat Cultures Postive for Beta Hemolytic Streptococci* | |
| | | *No.* | *%* | | *No.* | *%* |
| 1936-1937 and 1937-1938 ..... | 166 | 8 | 4.7 | 71 | 10 | 14.1 |
| 1938-1939 ..... | 136 | 7 | 5.1 | 100 | 12 | 12.0 |
| 1939-1940 ..... | 198 | 5 | 2.5 | 165 | 19 | 11.5 |
| Total for 1936-1940..... | 500 | 20 | 4.0 | 336 | 41 | 12.2 |

and night, or approximately 1.3 grams a day. With rare exceptions we gave the same dosage to everyone, regardless of body weight. Two or three of the youngest ones received only a gram a day for a number of months.

In the original study, fifty-five patients were treated prophylactically over a total of seventy-nine person-seasons, while sixty-seven control patients, thirty-two of whom had been treated in previous seasons, were observed over a total of 150 person-seasons. The results, both as regards inhibiting the beta hemolytic streptococcus and preventing rheumatic recrudescences were strikingly favorable. At each visit the pharynx of both treated and control patients had been swabbed in two different areas, the two swabs being immediately dropped into tubes of broth and promptly carried to the laboratory for culture. Twelve and two-tenths per cent of 336 such cultures made on the patients in the control group were positive for beta hemolytic streptococci. This incidence agrees well with that found in two studies on the carrier rate of the beta hemolytic streptococcus among normal persons living in Baltimore. Bourn, Carpenter and McComb[3] reported 10.4 per cent positive cultures among 2,812 persons, and Long and Bliss[4] found 10 per cent and 13 per cent positive pharyngeal cultures in two smaller groups of patients. In contrast, only 4 per cent of 500 pharyngeal cultures obtained from our treated group of patients were positive for the beta hemolytic

TABLE II

OCCURRENCE OF MAJOR RHEUMATIC EPISODES IN THE PROPHYLACTICALLY TREATED AND CONTROL GROUPS OF PATIENTS

| *Group* | *Person-Seasons* | *Major Episodes* | |
|---|---|---|---|
| | | *Number* | *Percentage* |
| Sulfanilamide | 79 | 0 | 0 |
| Control | 150 | 15 | 10.0 |
| Total | 229 | 15 | 6.6 |

streptococcus. This threefold difference was consistently noted throughout each season while sulfanilamide was administered.

The incidence of positive cultures in the treated group rose during the summer months while sulfanilamide was not given from 4 per cent to 18 per cent. This shows that the treated group was not inherently less susceptible to harboring the beta hemolytic streptococcus. It was also found that colonies of the hemolytic streptococcus were several times more numerous in the positive cultures of untreated than of treated patients.

None of the patients receiving sulfanilamide prophylactically suffered from any acute beta hemolytic streptococcus infection during the period of treatment. Two of the control patients had acute beta hemolytic streptococcus infections which were not followed by rheumatic recrudescences, and sore throats or markedly positive cultures or both preceded major rheumatic episodes in six of the ten control patients observed in the prodromal period. A seventh patient had many positive cultures during the rheumatic recrudescence but there was no sore throat and throat culture was negative at the onset.

During the four year study, not a single major attack of rheumatic fever occurred in any patient while taking sulfanilamide prophylactically. In contrast, fifteen major rheumatic episodes were observed among control patients during the same period, and five more control patients suffered from acute illnesses which might have been rheumatic in character. One boy who had taken sulfanilamide faithfully from October to June developed acute rheumatic fever in August, while he was not receiving treatment.

TABLE III

DISTRIBUTION OF MAJOR RHEUMATIC EPISODES BETWEEN TWO SUBDIVISIONS OF CONTROL GROUP

| | *Person-Seasons* | *Major Episodes* | |
|---|---|---|---|
| | | *Number* | *Percentage* |
| A. Had sulfanilamide other seasons | 84.5 | 8 | 9.4 |
| B. Never had sulfanilamide | 65.5 | 7 | 10.7 |
| Total control group | 150 | 15 | 10.0 |

Thus 10 per cent of the control group had recrudescences, while none of the treated group were affected. It apparently made no difference whether prophylactic sulfanilamide had been taken at some previous period, for the recrudescences observed in the control group were about equally divided between those controls who had had sulfanilamide in years past and those who had never received the drug.

The difference in the number of recrudescences between the treated and control group was great enough to be statistically significant. It appeared, then, that we had found real evidence to show that small daily doses of sulfanilamide have a prophylactic effect in preventing recurrent attacks of acute rheumatic fever. Toxic reactions, which I shall discuss presently, were negligible in our series.

Today I want to describe several interesting observations we have made during the year and a half since our four year study was completed, to correlate our results with those of others working in the same field, and in particular, to discuss a number of questions which arise in connection with this new approach to the treatment of rheumatic fever. In the season of 1940-1941 we accepted prophylactic sulfanilamide as a valuable medical procedure in the management of rheumatic patients, administering it to all of the patients in the previous study who desired to continue to take it as well as to any suitable new patients referred to us. In order to undertake other studies related to rheumatic patients, we gave up the burden of following a formal control group, although many rheumatic patients not on sulfanilamide therapy continued to come to the Cardiac Clinic. Of the twenty-five patients who received the drug prophylactically during the last year of our study, twenty-one

elected to continue it in 1940-41, and fourteen of them are still taking sulfanilamide this winter (1941-1942). We have therefore had the opportunity of observing nineteen patients who have taken sulfanilamide for three or more years. Of these, eleven have taken the drug for three years, four patients for four years, three for five years, and one boy who was in our first group, is now taking sulfanilamide for the sixth year.

S. R. entered the study in October 1936, at the age of seventeen, shortly after his fourth attack of rheumatic fever. He was the one who had an acute attack in August, after his second season of sulfanilamide, while he was not taking the drug. Since that recrudescence he has insisted upon taking the drug summer and winter, so that for the last four years he has never been without it. He had mitral stenosis and aortic insufficiency upon entering the study, without cardiac decompensation. Under treatment he has had no further acute rheumatic fever, his cardiac lesion has remained stationary, and he has worked hard at a factory job while attending night school to make up for the schooling he lost during years in bed. There is no evidence that the continuous use of sulfanilamide has undesirably affected either his mental or physical state.

The others who have taken sulfanilamide for long periods of time are in vigorous physical condition, have seemed unusually free from minor illnesses and most have been able to work hard or attend school or both, with the exceptions to be noted presently. There is no evidence of loss of weight over the period of years, and minor toxic reactions at the time of restarting the drug in the autumn have been notably absent. Several of these patients in addition to the boy mentioned have taken the drug summer and winter for two or more years. In view of our favorable experience, it now seems wiser to administer the drug the year around rather than giving the patient a summer vacation, since rheumatic recurrences may come at any season. This procedure, from a practical point of view, greatly lessens the work which is necessary when all the patients need to be started on the drug each fall.

We have had the first two rheumatic recrudescences in treated cases observed by us in the course of six years, one last winter and one this December.

G. B., a white girl of sixteen years, was admitted to the study in October, 1938, six months after her third attack of acute rheumatic

fever. She received prophylactic sulfanilamide for two seasons uneventfully, while she worked as attendant on one of the children's wards in the hospital. In October, 1940, she started to take sulfanilamide for the third season. She was married in December and took a factory job on the night shift. She found these new adjustments difficult and was fearful and under nervous strain. During the winter she had two slight colds without acute sore throats; the pharyngeal culture and sedimentation rate* were always normal at her regular clinic visits. On March 28 she was found to have well marked chorea and was admitted to the ward, where she remained seven weeks. At no time did she have fever, leucocytosis, elevation of the sedimentation rate, electrocardiographic changes or clinical evidence of acute rheumatic fever apart from the chorea. The beta hemolytic streptococcus was never cultivated from her pharynx. Prophylactic sulfanilamide was resumed three weeks before leaving the hospital without incident. She is taking it again this winter.

Here, then, is our first instance of major recrudescence in a treated patient. In this case the recurrence took the form of pure chorea, without any evidence of preceding beta hemolytic streptococcal infection. In view of the uncertainty of the etiological factors contributing to the appearance of chorea, we can only speculate as to whether sulfanilamide prophylaxis will prove to be effective in this particular variant of the rheumatic state.

This winter, however, we have had a definite flare-up of acute rheumatic fever occurring in a patient who was taking prophylactic sulfanilamide for the fourth season.

R. H., a negro boy of seventeen years, entered the study in January, 1939, ten days after discharge from the hospital ward where he had been for three months with his sixth attack of rheumatic fever in six years. He was given prophylactic sulfanilamide, which he took fairly conscientiously. Although he sometimes admitted skipping an occasional dose, he said he never omitted the drug for a whole day. He had been recently working as a junk man. On December 13, 1941, he was out all day in a sleet storm and became chilled and soaked to the skin. December 16 he had a pain in his back, felt badly and went to bed. Three days later his left knee began to hurt. He came to the Cardiac Clinic the next day, where he was found to have fever, tachycardia and a

* Sedimentation rates were done by the Wintrobe method.

swollen fluctuant left knee joint. He was admitted to the hospital. There was no story of sore throat and on admission his pharyngeal culture was negative for beta hemolytic streptococcus, although a few colonies had been present several weeks before. His temperature reached 104.5° the day of admission, his sedimentation rate was 26 mm. in an hour. On acetylsalicylic acid his temperature fell to normal in thirty-six hours, his pulse rate subsided. No further joints became involved, his sedimentation rate became normal and remained so at the end of the first week. Serial electrocardiograms showed slight prolongation of the P-R interval on the fifth day, which promptly disappeared. Prophylactic sulfanilamide was resumed twenty days after admission and two days later he was discharged. He has been resting at home since, feeling perfectly well. His sedimentation rate has remained normal.

Here, then is a definite instance of failure of sulfanilamide to protect. Although one can hardly expect a perfect record from any form of therapy, it is worth pointing out that this attack was apparently mild, and of brief duration.

In addition to the patients who first started sulfanilamide as part of the study, we have given it to ten or twelve other patients in the course of the past year and a half. Since they began the drug at varying times of year, we have not added them to the patients of the original group who have received a total of 114 patient-seasons of sulfanilamide treatment.

It is now our custom to start giving prophylactic sulfanilamide to convalescent rheumatic patients a few days or a week before discharge from the hospital. We think this important because several patients, who were discharged from the hospital with negative pharyngeal cultures, returned to the Cardiac Clinic two or three weeks later with a heavy predominance of beta hemolytic streptococci in the cultures then taken, indicating prompt re-invasion by that organism as soon as the patient returned to his home surroundings. We have had no difficulty in administering sulfanilamide to patients who are afebrile and asymptomatic after salicylates have been withdrawn, and we have not found it necessary to wait for the sedimentation rate to return to normal.

Let me now refer to other interesting studies which have been carried out on this subject. In the same year that we began our observations, Coburn and Moore[5] started to give sulfanilamide prophylactically to several groups of rheumatic children both in a convalescent home and

in regular and special schools in New York City. In 1940 they reported[6] that only one out of 184 subjects thus treated had developed rheumatic fever. In 1939, they observed 129 untreated adolescents and young adults as a control group and noted a 20 per cent incidence of rheumatic attacks, while in 1938 and 1939, 35 per cent of a smaller untreated group of children suffered from recrudescences. They also noted a striking difference between treated and control groups in the presence of the hemolytic streptococcus and streptococcal infections.

In the last two years several investigations of the same question have been undertaken, most of which are still in the process of completion. This is most encouraging, for it is of the greatest importance that the use of prophylactic sulfanilamide be studied under many conditions of age, climate, environment and general hygiene. Last winter, Kuttner[7] divided the convalescent rheumatic children at Irvington House into two equal groups, and gave sulfanilamide prophylactically to one group. None of the treated group had a rheumatic recrudescence and only one had streptococcal pharyngitis, while 30 of the 54 untreated children developed streptococcal pharyngitis and 14 of these subsequently developed clinical rheumatic recurrences. Four others showed laboratory evidence of rheumatic reactivation. This study, which Kuttner has already presented before the Brooklyn Academy of Pediatrics and which is soon to be published, is most convincing, for both treated and control groups were exposed to the same environment with little outside contact, and all were equally exposed to beta hemolytic streptococcal carriers within the convalescent home itself.

In the Bellevue Childrens' and Adolescents' Clinics[8] a large group of children have thus far been treated for 150 patient-seasons with no recurrences except in three far advanced cases. Chandler and Taussig[9] in Baltimore have had no recurrences to date among rheumatic children observed for 41 patient-seasons, and Roberts[10] in Philadelphia has had equal success with a similar group. Stowell and Button[11] in New York City found that sulfanilamide appeared effective in protecting against recurrences of rheumatic fever, but reported unfavorably upon the toxicity of the drug, with one death from agranulocytosis.

Here is a summary of the work done by the groups mentioned, three of whom have most kindly permitted me to refer to their studies while they are yet in progress (Table IV). Fortunately, sulfanilamide was the drug used throughout; no other sulfonamide drug has thus far been

TABLE IV

SUMMARY OF STUDIES ON THE USE OF PROPHYLACTIC SULFANILAMIDE IN RHEUMATIC FEVER

| *Author* | *Type of Patient* | *Age of Patient* | *Years of Study* | *Daily Dose of Sulfanilamide* | *No. of Patient Seasons* | *Results* | *Toxic Effects* |
|---|---|---|---|---|---|---|---|
| Thomas et al. | Clinic | 8-37 | 1936-1942 | Grams 1.0-1.3 | 114 | Excellent | Few and Mild |
| Coburn and Moore | Convalescent Home and Clinic | 6-14 | 1936-1940 | 2.0-3.0 | 189 | Excellent | 10% None Serious |
| Stowell and Button | Clinic | 11 (Average) | 1940-1941 | 1.5-2.0 | 46 | Fair | One Death |
| Chandler and Taussig* | Clinic | 6-16 (One of 20) | 1939-1942 | 0.6-1.7 | 41 | Excellent | Few and Mild |
| Kuttner* | Convalescent Home | 7-15 | 1940-1942 | 1.0-2.0 | 108 | Excellent | 15% None Serious |
| Bellevue* Childrens' and Adolescents' Clinics | Clinic | 8-17 | 1939-1942 | 1.0-2 3 | 150 | Excellent | Mild; None Sufficient to Stop Drug |
| | | | | | *Total (648)* | | |

* To be published.

tried in the prophylaxis of rheumatic fever to my knowledge. Several investigators have considered testing the value of sulfadiazine in this regard, but at present it would be very expensive to use it over months and years. Table IV shows that several hundred children and young adults have received sulfanilamide prophylactically for a total of 648 patient-seasons during the past six years. Thus far, only six have had rheumatic recrudescences, an incidence of less than one per cent. One of these recrudescences was pure chorea and three occurred in advanced cases of the chronic type. Recrudescences have been noted in from 10 to 35 per cent of the control patients, the incidence varying with age, from group to group and from year to year. Among the treated group we might therefore have expected at least 130 attacks (an incidence of 20 per cent) rather than six, if sulfanilamide were ineffective. By grouping together these studies the results mount up into an impressive body of evidence in favor of this method of treatment.

Although on casual inspection the dosage administered by the different groups seem similar, some groups have used double and almost triple the daily dose used by others. Thus throughout the first year we gave only 1.0 gram a day to adolescents and adults, and since then have given no more than 1.3 grams a day. Chandler and Taussig[9] gave a similar small dose. Coburn and Moore,[5, 6] on the other hand, gave 2 grams a day to small children, 3 grams a day to large children. Stowell and Button[11] gave 2 grams a day to all but the smallest children, those weighing under 55 lbs., which would be the six and seven year olds. The other two studies have used an intermediate dosage.

The concentration of sulfanilamide in the blood has been studied in each group and has been found to vary from 1.0 to 5.0 mgm. per cent. There is no theoretical basis for determining the minimal blood level which will provide adequate protection against invasion by the streptococcus. So far the amount of protection indicated by our clinical results and those of Chandler and Taussig, using small dosages, has been as great as that found in the groups where larger doses are used.

It is worth noting that these two "small dose" groups have had the least trouble with toxic reactions. In children, Chandler and Taussig observed transient rashes in three, mild gastrointestinal upsets in three, slight leucopenia in three. They have had no reactions severe enough to stop the drug permanently. All these mild symptoms appeared shortly after starting treatment, none appeared late in the course of treatment. Our experience has been with similar mild symptoms. We have not observed the transient anorexia and weight loss which Chandler and Taussig report as occasionally present after beginning the drug, and which Coburn and Moore mentioned in their first paper.

Only two patients in our group have stopped the drug on account of toxic reactions. One boy had urticaria and nausea and refused to continue taking it, although his symptoms were not serious. The second child, previously reported as reacting unfavorably to the drug, has since been able to take it and has done so for nearly a year.

N. S., a seven year old white boy, was started on prophylactic sulfanilamide, 0.9 gram a day, in January 1940, six months after his second attack of rheumatic fever. The day he first started the drug his leucocyte count was 19,150 for no obvious reason; three days later he had a cold and looked flushed, and on the seventh day the white blood cell count had fallen to 4,300 and he complained of fatigue. Segmented neutrophils

fell from 50 per cent to 28 per cent, while juvenile neutrophils rose from 5 per cent to 17 per cent. Sulfanilamide was stopped, and the leucocyte count gradually rose to 11,600 in the next eleven days.

Two more 0.3 gram tablets were administered, one at night and one the next morning. He again appeared flushed, so he was brought in and his leucocyte count found to be 14,200. The drug was stopped, and two days later he had 6,700 leucocytes with 38 per cent adult and 3 per cent juvenile neutrophils. The drug was discontinued for the year on account of the unstable leucocyte count, fatigue and flushing.

The next winter, in November 1940, he had his third attack of acute rheumatic fever and was in the hospital nearly three months. Toward the end of his stay in the hospital 0.3 gram of sulfanilamide was administered on two consecutive days. His leucocyte count remained unchanged around 11,000, but on the afternoon of the first day his temperature spiked to 101° for the first time in weeks, so the drug was once more discontinued. (A similar spike was observed a week later when he was not taking sulfanilamide.) In March 1941, after he had been out of the hospital a month, he was again cautiously started on sulfanilamide 0.25 gram a day in capsules. His leucocyte count was 7,700 and his polymorphonuclears 30 per cent, all adult forms, the day the medication was started. No significant change in total white cells occurred during three weeks; the neutrophils increased to 53 per cent. The dose was then increased to 0.5 gram a day. His count never fell below 5,000, and he now has taken 0.6 gram a day since August, feels well, and has a perfectly stable, normal leucocyte count.

Coburn and Moore[5,6] noted toxic symptoms in 10 per cent of the children under their care within a few days after starting medication. The patients who tolerated the drug for two weeks remained symptom-free thereafter. In the Bellevue Childrens' and Adolescents' Clinics,[8] no toxic symptoms serious enough to necessitate discontinuing the drug have been encountered. Kuttner,[7] on the other hand, has withdrawn the drug within five weeks of beginning treatment in 15 per cent of her patients on account of rash with or without fever, at times accompanied by abdominal pain, nausea and vomiting. She has also encountered leucopenia and decrease in the percentage of granulocytes.

Stowell and Button[11] observed toxic effects in 19 out of 46 patients treated prophylactically. In 25 per cent the drug was stopped permanently on this account. Persistent rash, fever, nausea and lowering

of the leucocyte count were the principal reactions. They also reported the first death from prophylactic sulfanilamide, due to agranulocytosis. A twelve year old boy had received 0.6 gram three times a day (or 1.8 grams a day) prophylactically for twenty-nine days when sore throat and fever developed. His leucocyte count was normal three days previously. Instead of being brought to the clinic according to instructions, a private physician treated him at home for two more days, during which time he received small amounts of the drug. On admission to the hospital he had ulcerative pharyngitis, high fever, 300 leucocytes per c. mm. of blood, with only 1 per cent polymorphonuclear cells. Blood culture was positive for staphylococcus and pneumococcus. He died on the fourth day after admission.

In discussing these undesirable reactions, let us consider nausea, rash and fever first, and then leucopenia and agranulocytosis. Nausea, fever and rash are disagreeable symptoms which are important in that they interfere with the prescribed treatment, but they do no serious harm to the patient. There is good evidence that they are more prevalent when large doses of the drug are given than when smaller doses are used. Stowell and Button noted two patients who developed rash on 1.8 grams a day which disappeared when the dose was lowered to 1.2 grams a day. I predict that few patients would need to stop the drug permanently on account of these symptoms if the smaller prophylactic dosage were used. Those patients who do show symptoms should stop the drug, resuming it after several weeks at a dose of 0.3 gram a day. This dose may gradually be increased to the desired total dose over several weeks. It may be that such graduated dosage administered to all patients beginning the drug would tend to eliminate toxic effects.

A number of us have observed a gradual lowering of the total leucocyte count during the first weeks of treatment, sometimes to levels between 2,500 and 4,500, with subsequent increase to normal without discontinuing the drug. Other authors have commented upon this as a benign and fairly common occurrence. The granulocytes may not be depressed, or may fall to 25 or 30 per cent. Since agranulocytosis does rarely occur, however, following sulfanilamide administration, the development of leucopenia must be watched for with the greatest care so that the drug may be discontinued whenever an abrupt decrease in leucocytes occurs.

Since Stowell and Button's[11] report of a case of fatal agranulocytosis,

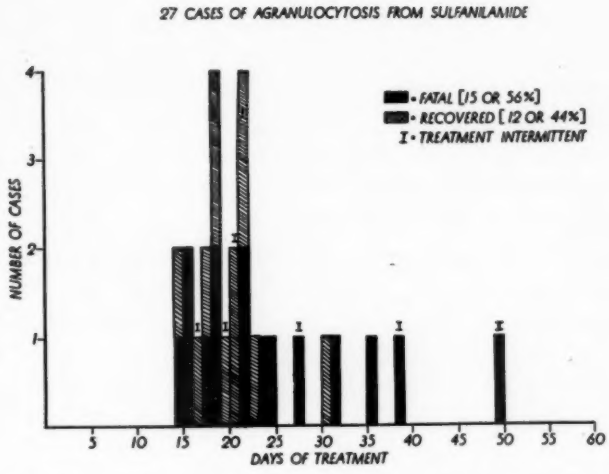


Fig. 1—For the cases charted in Figure 1 see references 11-36, i.. the order of length of treatment, with two exceptions. Garvin[19] cites two cases, one treated 14 days, the other 17 days. Stowell and Button's case[11] was treated 31 days.

I have reviewed all the available reports of agranulocytosis following sulfanilamide administration[12-36] (Fig. 1). Of twenty-seven cases thus collected, fifteen were fatal and twelve recovered. These cases are charted to show the total span of time in days over which sulfanilamide was administered, whether intermittently or continuously, between the day the drug was started and the last dose before agranulocytosis was discovered.

In considering these cases, it is striking that none occurred before the fourteenth day or after the forty-ninth day of therapy, and that all but two occurred within a span of three weeks time. Agranulocytosis developed most often after eighteen to twenty-one days of sulfanilamide therapy. (Agranulocytosis following the use of sulfapyridine or sulfathiazole appears at a similar time.) The dose of sulfanilamide does not seem to be the determining factor in the appearance of agranulocytosis, for while many of the patients received 3 to 6 grams daily, there were several fatal cases that received less than 2 grams a day. Again, agranulocytosis appears at about the same time interval whether the drug has been taken continuously or intermittently. An illustration of this fact appears in the case reported by Alpert and Forbes.[16] This patient

received sulfanilamide for seven days, then was given no more until the sixteenth day, when the drug was administered again for twenty-four hours; on the seventeenth day agranulocytosis was discovered. Whether agranulocytosis would have developed if sulfanilamide had not been given on the sixteenth day is an interesting question; it is not unusual for agranulocytosis to appear several days after the drug has been stopped.

In cases which subsequently develop agranulocytosis, the leucocyte count may remain within the normal range during the first two or three weeks or more of treatment. Thus, Stowell and Button's patient had 5,500 leucocytes on the twenty-sixth day of treatment, three days before sore throat developed; agranulocytosis was first discovered on the thirty-first day, but the exact day of its appearance is uncertain. Likewise, symptoms of toxicity may neither precede nor accompany the development of agranulocytosis, and ulcerative pharyngitis may never appear, even in fatal cases. A number of instances are reported in which the patients felt perfectly well for several days after agranulocytosis was discovered. In other cases, however, there have been fever, rash, vomiting or other toxic symptoms at some time preceding the agranulocytosis. These often occurred in the first week or so of treatment with large doses of sulfanilamide, and later, on a lowered dose, subsided some days before the appearance of the agranulocytosis. Since the same toxic symptoms appear in many more patients who never develop agranulocytosis, it can hardly be said that the one heralds the other. It therefore seems that while injury to the leucocyte forming mechanism may occur within the first two weeks of treatment, such injury is probably followed by a latent period during which it is impossible to foretell the imminence of agranulocytosis. It is during this period that frequent leucocyte counts are of great importance. How much further damage sulfanilamide may do when given after the onset of agranulocytosis remains to be determined; it may be pointed out that McGuire and McGuire's case[33] of agranulocytosis recovered even when the ulcerative pharyngitis was vigorously treated with oral and intravenous sulfonamides.

I have discussed agranulocytosis in detail to show that it appears to represent a sensitivity to sulfanilamide which very infrequently appears during the first few weeks of treatment. How rare it is may be realized when it is considered that this group of fifteen cases includes, with a few unavoidable exceptions, all the fatalities from this cause reported

here and abroad since 1937, while sulfanilamide has been used to treat hundreds of thousands of patients suffering from many kinds of diseases. Once the first weeks of treatment are safely passed, there appears to be no risk of agranulocytosis appearing, as shown by the fact that sulfanilamide has been given to thousands suffering from various chronic infections over periods of months without the report of a single late case. What I have said of agranulocytosis applies even more to other much rarer fatal effects of sulfanilamide which have never been encountered by workers on this particular problem. The risk entailed in giving sulfanilamide seems so much less than the chance of serious rheumatic heart disease developing if treatment is withheld, that I think we must accept that risk and, after proper precautions are taken, disregard it in order to treat the rheumatic patient to the best of our ability. There are, after all, few medical procedures of any therapeutic value which do not entail an element of risk.

Is the use of prophylactic sulfanilamide a practical possibility, or does it necessitate so many laboratory procedures that it can only be carried out in centers of research supported by special funds? Quite properly the initial work on this problem has been carried out with careful laboratory studies, but these were by no means all necessary to safeguard the welfare of the patient, nor to promote the therapeutic value of the undertaking. Antistreptolysin titers, pharyngeal cultures, sedimentation rates and electrocardiographic studies need not be undertaken in the routine care of rheumatic patients in the quiescent stage. It is not even necessary to carry out determinations of the level of sulfanilamide in the blood when the drug is taken in such small amounts, although two or three such determinations may well be done on each patient in the early months of treatment. Total white blood cell counts and hemoglobin determinations are the only routine procedures that must be carried out, and these should be followed carefully during the early weeks of treatment, supplementing them with other blood studies only when these simple blood counts are found to be abnormal. I wish emphatically to differ, therefore, with those who say that prophylactic sulfanilamide can be given with safety only in convalescent homes or specially endowed institutions; such a course would deprive the great majority of rheumatic subjects of the most promising weapon now available to combat rheumatic fever.*

* It remains to be seen whether sulfadiazine will prove equally effective and less toxic than sulfanilamide in this preventive role.

Is it possible to carry out a form of preventive medicine which necessitates the taking of pills every day for years by a person who feels entirely well? Sulfanilamide only gives protection while it is faithfully taken, and rheumatic recrudescences may occur after an interval of years. Since the greater part of the recurrences come within five years of the preceding attack, it would seem that five years would be the shortest span of time the drug should be taken, and for younger children the span should probably be longer. This is a difficult task, but with patience and perseverance in careful case following and education of rheumatic subjects and their parents, I think it can be done on a large scale as well as with a small group. Those individuals who have already had serious encounters with the disease are only too eager to carry out instructions. It is clearly far better to take sulfanilamide prophylactically for years and remain well, than to be forced to take digitalis for years after all chance of recovery is lost.

There are over a million persons in the United States who have suffered from rheumatic fever; 40,000 of them die each year of rheumatic heart disease. In these war years, rheumatic fever is important not only on account of its killing power; it burdens this country in many other ways. The initial phases of rheumatic fever disrupt a child's education by prolonged periods of illness and convalescence, and leave him unfit for the armed forces and for industry on account of organic cardiac lesions. In both the early and terminal phases of this disease long periods of bed care are necessary, involving the prolonged services of physicians and nurses as well as hospital facilities and convalescent homes, which are badly needed for defense purposes. Large sums of money from both public and private funds are expended in caring for victims of this disease and their dependents. The time to inaugurate a program for combatting rheumatic fever with prophylactic sulfanilamide is at hand, and to postpone it until after the war would be to lose sight of the immediate importance of this public health problem.

In this lecture I have pointed out that prophylactic sulfanilamide is effective in preventing rheumatic recrudescences, that it is relatively safe, and that if the routine is stripped to essentials, the cost is far less than the cost of caring for the cardiac invalids these rheumatic subjects would eventually become. An effort should be made to treat every individual who has had rheumatic fever early in the evolution of his disease with *small* daily doses of sulfanilamide and to continue treatment

over a period of years. When this is done, we may hope for real progress in controlling rheumatic heart disease in this country.*

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# THE EVOLUTION OF OUR PRESENT KNOWLEDGE OF HYPERSENSITIVENESS*

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IN the light of the fact that the hypersensitive reactions are often of startling intensity and the onset of symptoms most sudden, it is not to be wondered at that the noticeable contrast between the reaction of the idiosyncratic and other persons against one and the same agent has commanded attention from time immemorial. The condition of hypersensitiveness per se was recognized at a very early period.[1] Greek and Roman authors described the phenomenon by the term "idiosynkrisie" which is used today. Galen employed the term "idiopathy." The thought of the time, as is evidenced in this terminology, centered about attempts to gain an insight into constitutional deviations of the idiosyncratic, emphasis apparently being placed upon individual disposition rather than upon environmental factors. Though the dawn of the twentieth century ushers in the true beginnings of our present knowledge of allergy, we might pause a moment to reflect that no new discovery is ever so entirely original that it does not have its roots in the past.

Elliotson,[2] in London, in 1831, was the first to seek an etiologic factor in the pollens of the blossoming grasses. This work, taken up by Blackley[3] in Manchester in 1873, was greatly extended by the latter's use of the "skin and mucous membrane tests," inoculation of flower dust into scarified skin, and inhalation of pollen. Blackley's publication stated that a disease described by John Bostock[4] in 1819 as a "periodical affection of eyes and chest" and later as "catarrhus aestivus" was viewed etiologically as a "pollen catarrh" and that this was related to those idiosyncrasies which were known even in Galen's time as "rose cold." There was little opposition to the "pollen theory." Dunbar,[5] in 1903, confirmed the findings of Elliotson and Blackley and corrected the impression of the English authors on two important points, namely, that hay fever sufferers were hypersensitive during the non-pollinating sea-

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son, and, secondly, that there was a relative specificity of pollen idiosyncrasy.

Some of the early observations are of interest in showing how inevitable the discovery of anaphylaxis was with the introduction of the experimental method. Scattered communications appeared which were concerned with increased reactions produced by repeated injections of foreign materials. In 1890, Koch[6] first clearly demonstrated the phenomenon of hypersensitivity to a specific substance in his experiments with tuberculin. We glean from Morgenroth[7] that in 1839 Magendie observed that white rabbits easily tolerated a first injection of albumin but that some days later they could not tolerate the injection of a similar dose. Flexner[8] (1894), too, observed that rabbits, surviving a first injection of dog serum without a symptom, some days or weeks later died when given an equal or even smaller dose. Behring,[9] in 1893, studying the effects of diphtheria toxin on guinea pigs, showed that these animals, once injected with the toxin, became in certain cases intensely sensitive to it; but he did not consider the phenomenon either general among the injected animals or common to all poisons. Studying immunity particularly, he considered hypersensitivity a "paradoxical reaction." He made the statement that horses, under immunization, possessing large amounts of antitoxin in their blood showed hypersensitiveness to the toxin. These animals in all probability did not develop symptoms referable to the specific action of the toxin injected, for toxin is never injected in a pure state. The symptoms were, therefore, most probably due to the associated materials in the media. In 1894, Arloing and Courmont[10] noted that successive injections of donkey serum produced toxic effects in man. Courmont,[10] in 1900, noted that on inoculating guinea pigs with successive and very weak doses of the effusion of tuberculous pleurisy, the animals died before receiving a quarter of the total dose they originally took as a single injection, without ill effect.

These investigators did not realize that they had stumbled upon a phenomenon not heretofore described or named. It was Charles Richet,[11] the French physiologist, who in 1902 recognized the novelty of the phenomenon so many others had chanced upon yet did not comprehend, and it was he who correlated his observations and followed them out to their logical conclusions.

Yet, it is interesting to recall that in 1898 Richet[12] himself com-

pletely missed his opportunity while he and Héricourt were studying the effects of eel serum on dogs. He noticed that the second injection, and the third even more markedly, made them sick and waste away. Richet admitted later that he did not understand the significance of this result and contented himself with supposing there was increased sensitivity without attempting to analyze the phenomenon. Opportunity knocked at his door once again, which happens more often than we are ready to believe. As Richet[13] so aptly remarked in his book, "The Natural History of a Savant," one can work a life time on a problem and develop nothing of fundamental importance, yet occasionally one may chance upon a great discovery after but a short period of work. So it was with his discovery of anaphylaxis. He chanced upon a phenomenon in biology which bids fair to take its place amongst the great discoveries and for which he received the Nobel Prize. It has opened the door to the understanding of a host of conditions which afflict mankind. In this sense then we can say that the dawn of the 20th century is the true beginning of our basic knowledge of hypersensitiveness.

Richet's[14] discovery was made in the course of his study of toxins with which he attempted to immunize dogs. Animals which withstood the lethal dose were later again injected with the same toxin. It was these reinjection experiments which drew his attention to the peculiar phenomenon to which he gave the name "anaphylaxis." The experiment which led to his discovery will be briefly quoted here.

> "During a cruise on Prince Albert of Monaco's yacht, the Prince and G. Richard suggested to P. Portier and myself a study of the toxic properties of the Physalia found in the South Seas. On board the Prince's yacht experiments were carried out, proving that an aqueous glycerin extract of the filaments of Physalia is extremely toxic to ducks and rabbits. On returning to France, I could not obtain any Physalia and decided to study comparatively the tentacles of actinaria, which resembles physalia in certain respects and are easily procurable. Owing to the kindness of Y. Delage, I was able to obtain a large quantity; the tentacles cut close to the body were placed in glycerin and thus we had in Paris several liters of an intensely toxic fluid, the glycerin dissolving and extracting the active principle. While endeavoring to determine its toxic dose, we soon discovered that some days must elapse before fixing it, for several dogs did not die until the fourth or fifth day or even later after administration. We kept those which had been given a dose insufficient to kill, in order to carry out a second investigation upon them when they had completely recovered.
>
> "At this point, an unforeseen event occurred. The dogs which had recovered were intensely sensitive and died a few minutes after the administration of subsequent small doses.
>
> "The most typical experiment, that in which the result was indisputable, was carried out on a particularly healthy dog named "Neptune." He

> was given at first 0.1 c.c. of the glycerin extract without becoming ill; twenty-two days later, as he was in perfect health, I gave a second injection of the same amount. In a few seconds, he was extremely ill; breathing became difficult, and he was panting. He could scarcely drag himself along, lay on his side, was seized with diarrhea, vomited blood, sensibility diminished, and he died in twenty-five minutes."

It has always been a source of wonder to me that Richet should have discovered anaphylaxis with a substance that was highly toxic and that this discovery should have been consummated in the dog, for Weil[15] and others have since shown that anaphylaxis is difficult to induce in the dog.

Richet's observation was first attributed to toxin accumulation, and yet, he stated that the symptoms of this reaction differed greatly from primary intoxication studies. His systematic investigations revealed that the described phenomenon is produced at least 2 or 3 weeks after the first injection, which definitely excluded the cumulative concept. Richet determined that the first toxin injection in his animals not only caused no antitoxic immunity but rather that it produced an increase in the toxin sensitivity which was manifested after the course of a certain incubation period. The first toxin injection did not act "prophylactically" in these animals, but in contrast, as Richet termed it, "anaphylactically." The first toxin injection transformed the animals into a state of "anaphylaxis" (without protection).

On the heels of Richet's discovery came Arthus[16] (1903) who demonstrated that a non-toxic protein may also produce hypersensitiveness. According to the pioneer observations of Arthus, rabbits react neither to subcutaneous, intraperitoneal nor intravenous primary injections of horse serum. On the other hand, when rabbits previously sensitized to horse serum are reinjected intravenously, very severe symptoms appear almost immediately which may lead to anaphylactic death in two to four minutes. If the horse serum is injected subcutaneously at six-day intervals, resorption of the serum takes place after the first three of such injections. However, after the fourth injection, infiltration appears which finally develops into necrosis, sequestration and abscess formation. This, Arthus described as local anaphylaxis, known today as the "Arthus Phenomenon." The use of the terms "local" and "general" anaphylaxis leave no doubt that Arthus identified his observations with those of Richet.

His experiments were successful not only with horse serum but also

with cow's milk. However, rabbits sensitized with the one substance were unharmed by the other, thereby demonstrating the specificity of anaphylaxis. Since Richet and Arthus resorted to such varied stuffs as the toxic actino congestin and nontoxic cow's milk and horse serum, it became evident that anaphylaxis could be produced with substances which are very different from each other in chemical properties and in physiological action.

Many substances and various animal species were subsequently used to demonstrate anaphylaxis and yet, not until the guinea pig was utilized were really decisive results obtained. The guinea pig became the experimental animal of choice in this field after Theobald Smith[17] made the following observations (1905). In the course of his work on the standardization of diphtheria antitoxin, Smith noted that guinea pigs, which several weeks before had received a dose of diphtheria toxin and antitoxic horse serum, showed severe symptoms or died immediately after reinjection with several cc. of normal horse serum. Ulrich Friedemann[18] who was working in Ehrlich's laboratory informs me that although such reactions in guinea pigs to repeated injections had been observed for some time, no particular interest was evoked until Ehrlich returned to his laboratory in Germany after a visit to Smith in America. He suggested to Otto,[19] one of his assistants, that he work on this problem. Otto called it the "Theobald Smith Phenomenon." One is tempted to feel that Otto, the German, preferred to credit an American rather than the Frenchmen, Richet and Arthus, with this fundamental discovery.

Because of the ease with which this phenomenon could be produced in the guinea pig, the work stimulated by Smith awakened a tremendous and widespread interest in the subject of hypersensitiveness. The same conclusions as Smith's were drawn by Rosenau and Anderson[20] in America, and in rapid succession by many others.

The first recorded foreign serum injection into man, that of lamb blood, was given in 1667, by Deins.[21] No ill effects were ascribed to this introduction of foreign serum, until the beginning of the 19th century, when the intravenous introduction of lamb blood was discovered to be accompanied by grave danger, resulting in high fever, emboli, bleeding and hemoglobinuria. The cause for these reactions was first explained by Landois[22] and Ponfick, in the latter part of the 19th century, but their explanations were concerned with incompatibility of blood cells. At about this time, urticarial eruptions were observed to occur several

days after transfusions. Dallera[23] described a case of a girl with "hysterical mania" whose whole body was covered with urticaria ten days after transfusion. Other reports soon followed. Because of the ill effects of lamb blood transfusions, animal blood transfusions were almost completely abandoned. Dominicis,[24] in 1895, tried to revive their use. Milk transfusions were also attempted but soon disappeared from medical annals because they were found to be useless and dangerous.

Since Pasteur's discovery, in the middle of the 19th century, that infectious agents are the cause of certain diseases, attempts have been made to aid the body in specifically neutralizing invading bacteria and accelerating the mechanism of immunity. This has given rise to the use of antitoxic and antibacterial sera obtained from other animal species. In 1894, the treatment of diphtheria with antitoxic horse serum had been introduced by Behring.

Lublinski[25] was probably the first to publish a case of exanthem after the injection of a therapeutic serum. An eight-year old girl, on the second and third days of her illness, received injections of 0.3 cc. Behring's diphtheria antitoxin. On the fifth day of her illness there was a red area around the site of the injection. Nine days after the last injection she developed high fever, multiple and painful joint swellings with a widespread multiform erythema and a macular eruption. This severe syndrome lasted for four days. With the recession of the exanthem the joint pains and swelling diminished.

Experimentally Johannessen[26] gave proof that the active agent in the production of these sequelae was not inherent in the antitoxic content, but something in the horse serum itself since the same symptoms were produced in non-diphtheritic persons with normal horse serum. A large number of publications appeared in the literature with respect to this syndrome which was called "serum exanthem" because of the cardinal symptom of skin eruption.

But no careful analysis of this condition was made until von Pirquet and Schick[27] published their classic monograph in 1905, "Serum Krankheit." The new term, serum sickness, included all the other symptoms besides the exanthem. They explained the clinical manifestations in the following way. Foreign serum acts on man as an antigen. Antibody, which develops in the organism as a result of the antigen, upon union with the horse serum produces the symptoms. Serum sickness is therefore an in-vivo, antigen-antibody reaction. The incubation period de-

pends upon the completion of the appearance of the antibodies and the presence of horse serum still remaining in the blood.

An important step in linking up the mechanism of serum sickness with allergy was the work of Hamburger and Moro[28] who, in 1903, demonstrated that precipitins resulted after the introduction of foreign serum.

Little notice might have been taken of the experiments of Richet and Arthus on anaphylaxis in its application to man had not von Pirquet and Schick found that *reinjection* of serum at some later date results in immediate and accelerated reactions, which phenomenon they called "allergy"—altered reaction. Charles Richet did not easily forgive von Pirquet for coining the term allergy, for, he argued, is not anaphylaxis sufficient to describe the phenomenon in both animal and man? One can appreciate his feelings, but usage and euphony have given to allergy the greater popularity. Furthermore, von Pirquet[29] used the term allergy in a broader sense than Richet, who considered anaphylaxis only from the standpoint of hypersensitiveness to foreign proteins. von Pirquet included all reactions to foreign proteins and infectious agents and laid the groundwork for our understanding of the relationship between allergy and immunity. One is in the best of company, however, whether one adheres to the term allergy, or prefers anaphylaxis.

The immediate character of the anaphylactic reaction described by Richet and Arthus would therefore in the light of von Pirquet and Schick's work be explained on the basis of the presence of previously formed antibodies. This conception of serum sickness and anaphylaxis as vital antigen-antibody reactions has served to elucidate many varied phenomena which at first appeared widely divergent but were later shown to depend on this basic concept. In the short period between 1902 and 1910 practically all the principles of hypersensitiveness were laid down.

One cannot deny that many diseases have been controlled through the use of antisera, but in their wake have come not only the relatively harmless serum disease, but the more serious serum allergy and anaphylaxis. Though the reaction to the invasion of foreign materials is purely a physiological one, the tempo of reaction is invariably accelerated. A knowledge of these reactions should lead to a more intelligent management of disturbed conditions that result paradoxically from a beneficent curative procedure.

For practical clinical purposes—so far as danger to life is concerned—

primary contact with foreign substances should always be carefully distinguished from secondary or repeated contacts. But, whether primary serum sickness or serum allergy are under consideration the basic similarity of their mechanisms must be kept in mind. Thus after primary contact with a foreign substance nothing transpires until an incubation period elapses, during which time specific antibodies are formed. When this supervenes, the foreign substance still present in the body reacts with the newly formed antibodies and the signs and symptoms of serum sickness become manifest in the different tissues. On the other hand, by allergy is meant the reaction which ensues when antibodies are present in the tissues as a result of previous contacts and when the specific antigen again enters the body a reaction takes place immediately or shortly thereafter without a prolonged incubation period.

Whether the invading foreign substance is a serum, food, inhalant, drug, or hormonal extract, the body response in each instance is fundamentally the same, differing only with respect to the tissues directly involved. From all of this, it must be apparent that the organism is so constructed that it continually impedes the invasion into the circulation of materials that cannot be utilized by the body economy. There are periods, however, when the organism fails to prevent the entrance into the body of inimical agents, such as bacteria, viruses, chemicals, toxins, and foreign proteins. When such invasions of foreign agents do occur, the organism may become either (1) damaged or destroyed, (2) allergic, or (3) immune.

There is a growing impression that allergy inevitably precedes a state of immunity.[30] Immunity, however, is not static, and an individual immune at one time may again become allergic. These changing conditions in the same individual depend largely on whether the antibodies are anchored to cells alone—the allergic state, or whether the antibodies are present in greater abundance in the circulation, neutralizing the antigen before it reaches the antibody containing cells—the immune state.

Another factor of great importance is that when the invasive substance is a viable antigen, such as a bacterium, it multiplies in the body and thus complicates the situation by destroying tissues through the production of endotoxins and exotoxins. On the other hand when the substance is not viable—serums, foods, pollens, etc.—and therefore nonmultipliable, no destructive lesions result, and the reaction is dependent entirely on the actual amount of antigen which invades the body at that particular time.

The evolution of our present concept of allergy is thus unfolded. But a small part of the story has been told, as may well be imagined. Some may question my omission of such developments as the anaphylotoxin theory, the protein cleavage concept, atopy, the histamine basis for allergy, the Schultz-Dale phenomenon, Otto's and others' work on passive anaphylaxis, the heterophile studies by Friedemann and others, the work emanating from the Prausnitz-Küstner phenomenon, and our own work on congenital hypersensitiveness and experimental asthma. My main purpose, however, was to show that this subject—whether we speak of it as hypersensitiveness, allergy, anaphylaxis, atopy or any other term that has been devised—is not young. The course of its growth has not been direct, and amongst the deviations have been the developments above named. Each has undoubtedly added something to our general knowledge, but to them we must assign a minor role.

As I see it, the major role in this ubiquitous drama is played by the antigen-antibody tissue reaction. We may sum it up simply as follows. A substance, foreign to the body economy, which in and of itself is harmless when entering the body for the first time, may produce a disturbance upon subsequent invasion. This is due to an interaction between the specific antigen and its related antibody which has been elaborated and become fixed to the smooth muscle cells of some organ or organs in the interim between the primary and secondary invasions of the antigen. The union produces cellular irritation with concomitant spasm and probable physico-chemical reactions of the sensitized tissue.

The type of syndrome produced depends upon the characteristics of the tissue irritated. Such a unitarian concept is supported by a wealth of sound observation. It enables us to conceive how such varied syndromes as serum sickness, eczema, hay fever, asthma, disturbances of the gastrointestinal tract, central nervous system, the liver and other organs, are all manifestations of the one phenomenon—a simple union of antigen and antibody with differing chemical, physiological and pathological secondary effects.

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# DIAGNOSIS OF THE ETIOLOGICAL FACTORS IN FEMALE STERILITY*

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DIAGNOSTIC study of sterility nowadays implies the clinical investigation of husband and wife and includes consideration of all genital factors as well as constitutional factors which may have an etiological bearing on the fruitless wedlock. This seems a far cry from the first decade of the present century when it was common practice to consider only the female in deciding the question of childlessness. The patient was subjected to routine bimanual examination which was as likely as not to include inspection of the vagina and the cervix, and perhaps occasional exploration with a uterine sound. The decision of sterility or fertility was based upon such routine gynecological examination which sought mainly to exclude gross abnormalities. It is no wonder that the prognosis was as often wrong as right.

The past twenty years have witnessed considerable progress in this field. First in chronological importance was the growing recognition that the male partner may be and often is responsible for the failure to conceive. This notion became better established as a fact through the work of Huhner who devised his biologic compatability test. Thus arose the idea of a sterile mating in contradistinction to the sterile mate. So important did this concept appear to us that a Huhner test was resorted to before proceeding with detailed examination of the status of the female.

The second step was the determination, by a clinical test, of patency of the upper portion of the female genital tract, namely the fallopian tubes, thus obviating the necessity of resorting to laparotomy for that purpose. Incidentally the patency of the cervical canal and uterine cavity was also ascertained. The method paved the way for biochemical and biodynamic research in the field of sterility.

The third step was the recognition of the importance of the constitu-

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tion of each of the married partners.

The fourth step was the development of our knowledge of hormones. The pioneers and workers who have made noteworthy contributions in this field are too well-known to be dwelt upon in this presentation.

Present day investigation of a sterile couple involves procedures that have come into practice in the last twenty years and has become a highly specialized chapter in gynecology, urology and general medicine. It calls for teamwork and correlation of studies undertaken in the various fields of medicine and biology. Some of the etiological factors are precise and reliable, others are not so reliable; some leave no doubt as to the factual data obtained, while others yield data whose interpretation leaves much doubt. In some directions we may have gone far afield and subjected the couple to unnecessary and useless procedures. In the present paper an attempt has been made to evaluate and appraise the etiological factors as well as the diagnostic procedures employed.

The causes of female sterility may be said to be local and general and they may also be considered as of major or minor importance. Of the local causes the more common are mechanical as opposed to functional. The latter are bound up with disturbances of the endocrine and nervous systems and with certain constitutional conditions. The mechanical causes are obstructive, due to anatomical dislocations, or for the most part pathological alterations of the genital apparatus. According to S. W. Meaker who analyzed seventy-five sterile marriages from this viewpoint, the constitutional factors play almost an equal role of importance with local genital factors. The local factors were found by Meaker in the proportion of 4 to 3 of the constitutional factors. In the experience of different observers the proportion may vary but in any event the constitutional factors will be found to play an important role in sterility.

Amongst the constitutional factors are chronic infections of the tonsils and sinuses with their systemic effects; thyroid dysfunction; syphilis; protein starvation; vitamin deficiency; alcoholism; and diabetes. Lead poisoning is a systemic condition which I have occasionally encountered in the husband. Hypertension, in my experience, has appeared to exert more of a deleterious result upon an existing pregnancy than upon the ability to conceive. These patients are predisposed to habitual abortion.

The causative factors of sterility, as Meaker has repeatedly pointed

out, are apt to be multiple. The local factors in the female outweigh similar factors in the male. According to Meaker the ratio is 4 to 1, whereas the constitutional factors are about even. I have not had occasion to check the relative incidence of these factors but there can be no doubt of the importance of the constitutional status in all cases and in many cases to a decisive degree.

Although an absolute cause of sterility as azospermia or ablated tubes may at once be established, it may in many instances be considered worthwhile to determine associated factors in order to decide the important question whether corrective procedures should be undertaken at all.

Unless something can be done about restoring spermatogenesis for example or tubal patency it would seem idle at first sight to proceed with any further exploration of the other factors. Nevertheless, it is only by most careful analysis of the constitutional condition, including associated circumstances that the possibility of restoration of function can be accomplished. Moreover, the normal mate may wish to achieve a child by remarriage. The request may be made for artificial insemination using the fertile semen of a known or unknown donor. If neither of these alternatives is chosen, the couple may wish to submit to a complete investigation with the end in view of adopting a child in case there is no hope for offspring of their own.

An individual of a markedly diminished fertility mating with another of more or less the same lowered fertility will be unlikely to be fruitful. If cross mating in the human family were possible, we should be in possession of data that would prove exceedingly helpful. This limitation in our knowledge prevents us from properly advising individuals whose keen desire for offspring prompts them to seek divorce in order to remarry. Obviously we cannot give such individuals assurance that the second marriage will prove fruitful. The potential fertility or sterility of the mate can only be proven by coital relations.

In the majority of instances there is more than one fault in both partners. Theoretically, by correcting one or several in the one or other mate, fertility should be enhanced; the deficiency of the one being compensated by the adequacy of the other.

The threshold of fertility varies not only with different individuals but in the same individual at different times. In women there is the absolute prepubertal sterility except in rare cases of precocious sex de-

velopment; there is further the relative sterility of lactation and its final establishment in the menopause. Relative infertility undoubtedly occurs in the same individual at various phases of the menstrual cycle. There are a few human comparisons with the famous bull (Sybil Gamboges) who could serve three different cows every day of the year and fertilize all of them. In the human sphere there is no doubt that the one individual enjoying a higher degree of fertility compensates for the relatively lowered fertility of the other partner.

Estimating the degree of fertility is obviously difficult. One cannot speak of it in mathematical terms. The highest degree of fertility may be seen in a married couple where the first exposure results in pregnancy and where conception follows every first time they choose to have another child, only one sex act being necessary to be fruitful. Each mate of this hypothetical fertile couple may be assumed, all other factors being equal, to be fruitful in another marriage with a partner enjoying equally high fertility or relatively diminished fertility. On the other hand, despite complete absence of detectable barriers, some couples remain childless for years although every artificial aid has been employed.

The evaluation of these factors is difficult except in a few categories. They may be said to have major or minor importance. Some are obvious while others are difficult to estimate, e.g., gynaplasia, azospermia, tubal occlusion, impotence, are factors of major importance that are quickly discovered. Minor factors are not so obvious, yet they may at times assume major importance as, for example, when it is accidentally discovered that douching invariably follows the sex act because the patient believes she must cleanse herself promptly. Effluvium seminis may similarly defeat attempts at fertilization especially when the amount of semen is primarily deficient.

The deterrent factors are recognizable in about 90 per cent of cases of sterility. This does not mean, however, that the faults are all amenable to corrective measures. Nor does restoration to the normal average necessarily assure fertility. Until we learn more about the chemistry of reproduction we shall probably not be able to explain why many married couples remain infertile despite the fact that they have only minor faults or no appreciable stigmata. This fact should make us pause in prognosticating the chances of success for any proposed therapeutic measure.

As in all clinical diagnosis, a comprehensive medical history is ex-

tremely useful. This includes reference to impregnation in marital or extramarital relations; the termination of the pregnancies and character of the puerpera or abortions. Thirty-five per cent of 307 patients in my series who gave a history of artificial abortion proved to have tubal closure; an additional 22 per cent showed impaired patency. A history of gonorrheal infection is significant, as is the history of other infectious diseases especially mumps. In the female the effect upon the gonads of this infection is not as clearly manifest as in the male but that it exerts a harmful influence upon the ovaries is highly probable. Appendicitis has undoubted etiological importance in the female especially where pelvic peritonitis has occurred. Tubal occlusion and impaired patency were found by uterotubal insufflation in over half of 487 women complaining of sterility who gave a history of appendectomy. More specific is the record of pelvic inflammation and so-called abdominal influenza. Urinary symptoms especially right after marriage are suggestive of a Neisserian infection even when this is not affirmed by the patient. It has been shown to be the precursor in a number of cases of sterility due to tubal occlusion. Details of sex life with reference to libido, orgasm and habit; frigidity and dyspareunia are also of interest. It is amazing at times to what extent ignorance of sex hygiene on the part of otherwise intelligent individuals shrouds the sex act. Contraceptive methods undoubtedly affect fertility for longer or shorter periods after their use has been stopped. The duration of involuntary sterility is also of interest in relation to the general question as to how much time should be considered adequate to stamp a marriage sterile or infertile. The onset of menstruation, its character in adolescence, after marriage and after pregnancies, its duration, all in careful detail are of particular importance. Amenorrhea, oligo- and opsomenorrhea are very frequently associated with infertility. Not only is the number of theoretical ovulations reduced under these circumstances but the depressed menses indicate abnormal ovarian function and depressed constitutional states. Effluvium seminis is perhaps not as important a factor as was formerly claimed for it, but in some cases it may assume major importance.

Only a few remarks with reference to the Huhner test which has become more or less the special task of the gynecologist.

The finding of ample numbers of motile spermatozoa with good morphologic characteristics pretty nearly exonerates the male from being responsible for the infertility. It is the best evidence of his potency—

mechanical and generative. With this finding no further examination of the semen is necessary and one can proceed to inquire into the other factors involved in the infertile female.

If, however, the cervical and vaginal smears show few or no spermatozoa, examination of an unmixed semen becomes necessary. If the latter shows evidence of normal production as to amount of secretion, numbers of spermatozoa and with respect to their morphological characteristics, one may conclude that there was some interference with proper intromission or, what is less common, the semen was expelled from the vagina immediately after ejaculation. Detailed inquiry into the sex act usually discloses the fault in one or the other or both partners.

If, on the other hand, there is an abundance of spermatozoa in the vaginal secretion, most of which are dead, and none or a few are to be found in the cervix, it is evidence that the vaginal secretions are hostile, thus affording little or no opportunity for the spermatozoa to reach the cervical canal. It is rare to find abundant numbers of normally motile spermatozoa in the vagina and none in the cervix.

Without going too far into this inquiry one may say that the more copious the seminal ejaculate with its proportionate sperm content the more likely is conception to take place. Semen deficient in amount and in sperm content is less likely to be fruitful, all other factors being equal. The hazards confronting the spermatozoa in the lower portion of the genital tract require a surfeit to make up for the losses. A common mistake is to state that it takes but one spermatozoon to impregnate the ovum. One spermatozoon sent on its way from its source would stand one chance in two or three hundred million of reaching the goal.

In the physical examination search is made for conditions especially that interfere with the sex act, with the proper reception of semen, with factors that would be hostile to spermatozoa and impede their ascent to the tubes where they ultimately meet the ovum. Such deterrents may be seen in malformations and deformities; in the presence of infection of the urethra, vagina, Bartholin glands and cervix. Though spermatozoa can retain their motility in pus, the associated dyspareunia, secondary effects upon the male as well as cervical blockade can interfere with sperm migration. Malpositions of the cervix may interfere with favorable reception of semen and sperm ascent. Ulcerations of the introitus and vagina, unless chronic, and these are rare, may be responsible for failure of consummating the sex act. Stenosis and endocervicitis are common

deterrents. Cervical hypoplasia is in itself no hindrance. The cause lies deeper and is traceable to possible ovarian hypofunction. Adherent retroversion and retroflexion are frequently associated with adherent and strictured fallopian tubes which are more responsible than the uterine dislocation. Movable retroversions and retroflexions are not essential deterrents. Uterotubal insufflation has proved valuable in estimating the etiological importance of the distorted uterine position. Adnexal masses especially when tender, and tenderness alone, are other easily demonstrable etiological factors. When non-tender adnexal masses are present, tubal insufflation may serve to differentiate between ovarian cysts and hydrosalpinges, patent tubes pointing to the former. Retention cysts of the ovaries and dermoids are the only palpable lesions which have practical significance in relation to sterility. Other disturbances referable to the ovaries which may bear upon the problem of sterility such as hypofunction due to small ovaries, failure of corpus luteum formation, cannot be determined by the bimanual examination. Normal ovaries are not invariably palpable and small atrophic ovaries escape palpation most frequently. Malignant tumors of the ovaries seldom enter into consideration in this connection. I do not recall a single instance where carcinoma of the ovaries was accidentally met with in a case coming for the relief of sterility.

Regarding the ovaries in general and ovulation in particular, only secondary and conjectural data are available. The assay of excretion of sodium pregnandiol as advocated by Brown and Venning which gave much promise at first was not proven completely reliable according to Hamblen. There is as yet no one test or correlated reliable tests or direct evidence of ovulation except during laparotomy when inspection of the tube contents can be made.

An idea of the ovarian influence on the tubes and indirectly also of the pituitary influence may be obtained by kymographic uterotubal insufflation. The tubal muscle which is always under the influence of estrogenic stimulation has been shown to exhibit, in experimental animals, an increasing number of rhythmic contractions per minute, the force and frequency of which are increased during ovulation. In the human female rhythmic contractions of varying frequency and amplitude can conveniently be recorded by uterotubal insufflation throughout the postmenstrual interval. Correlating the clinical observations with the work of Seckinger and Snyder on the extirpated surviving human

fallopian tubes, it may be said that the character of the contractions in general reflect the degree of estrogenic stimulation and function. In many cases when this test has been carried out during the mid-menstrual interval, the contraction force and frequency suggested hypermotility which may have been coincidental with ovulation.

This evidence added to that obtained by appropriate staining of routine vaginal smears as carried out by Papanicolaou and Schorr can give an idea of good or deficient estrogenic function. They cannot however be construed as positive diagnostic evidence of ovulation. Electro-potential determinations, temperature measurements and other biodynamic methods have so far not proven reliable nor have the painstaking bioassays of hormonal excretion established definite criteria for determining the exact date of ovulation of any menstrual cycle. It would prove very helpful were it possible in a sizable series of cases to correlate such bioassays and vaginal smears showing cyclic changes and tubographs obtained by peruterine insufflation with actual inspection of the tubes and recovery of the ova from them.

Regarding the endocervical secretion, the best evidence of its normality is the effect exerted upon the spermatozoa. If motile normally appearing spermatozoa can be recovered from the cervical canal, it is evidence that they have encountered a favorable environment. If nonmotile spermatozoa are uniformly recovered from the cervical canal, although motility is demonstrable in the vaginal secretion, the cervical secretion may be said to be hostile. The nature of the hostility is not always determinable. The pH (hydrogen ion) value may be within physiological limits–pH 8.0, pH 9.0, the viscosity may be regarded as normal and the stained smear may show no specific changes. In other words, we are not in a position as yet to determine the nature of the lethal factor which the spermatozoa encounter in the cervical canal in any given case. It is not unlikely that there is some, as yet undetermined, substance in the serum or the mucus or the cellular content in the cervical secretion which paralyzes the motility of the spermatozoa, at least of that particular mate, preventing their ascent to the upper portions of the female genital tract. I have had occasion to examine the cervical secretion in the same woman after she had intercourse with several men and found the same relative hostility to the spermatozoa. Further work in immunology including the rH factor recently discovered may throw light on the antagonism of the cervical secretion which has proven the

burial ground for countless spermatozoa.

For practical purposes the physical examination of the uterus affords a clue to the normal or subnormal activity of the ovaries. A hypoplastic uterus usually bespeaks subnormal ovarian activity. A well-developed uterus indicates good ovarian function. If there is associated menstrual deficiency (oligomenorrhea, opsomenorrhea) with a hypoplastic uterus it is fairly presumptive evidence that the genital muscular tube is not receiving adequate estrogenic impulses. In my experience a rugous, short vaginal portion of the cervix with more or less quadrangular margins instead of the circular or elliptical margins is pathognomonic of infantilism. Such a vaginal portio has not developed completely and resembles the infant's portio vaginalis as I have had the opportunity of observing by the vaginal endoscope in several hundred cases.

The endometrium has telltale value with respect to the endocrine effect of the ovaries and anterior pituitary. But for this an examination of the uterine curettings is necessary. In the past ten years curettage has been replaced by the more convenient endometrial biopsy. The best time for taking an endometrial biopsy, if it is to be carried out once, is two or three days preceding the next ensuing menstrual period. If a pregravid endometrium is found, it is *strong presumptive evidence* that the ovulation-menstruation process is in order and that ovulation has been followed by corpus luteum formation. The endometrium has been prepared for the reception of an ovum. Whether this happens only in the presence of a fertilized ovum or regularly when the ovum is unimpregnated, as in the virginal state, has not been established. The absence of the predecidual or pregravid type of endometrium has been assumed to indicate that menstruation was not preceded by ovulation, in other words the bleeding is said to be anovulatory. On the other hand it must be remembered that the administration of estrogenic hormones followed by progesterone can produce in the menopause pregravid like changes in the endometrium. Furthermore, it has been found lately that stilbestrol alone can initiate the secretory type of endometrium in some cases during menopause.

Since practically all the investigations with endometrial biopsy have been carried on in married women, it is not possible to state in how many cases an ovum may have been impregnated and been blighted in its incipiency thus producing no actual delay in the menstrual period. If it were possible to obtain a pregnancy reaction in its incipiency, i.e.,

a day or two after impregnation instead of waiting till the next menstrual period has been delayed, it would help to clear up much of the question of ovular vs anovular menstruation. E. Novak has had the opportunity of studying the endometrium in girls with essentially normal menstruation and was convinced that it can occur from an endometrium of non-secretory type. This theory could possibly be further explored best by carrying out endometrial biopsy in a group of cases where the husband is definitely sterile and the wife faithful to her marriage vows.

An inherent limitation of endometrial biopsy, as of bioassays of hormones, is the fact that its data indicate what has taken place the particular month in which it was done. The findings of one month do not hold for the next or any other month. The same criticism holds true for hormonal assays as well as for vaginal smears. Endometrial biopsy has the disadvantage of possibly interfering with a very young pregnancy which is lamentable in the case of the infertile woman. For this reason it should be undertaken only when abstinence has been maintained during that particular menstrual cycle.

Dysmenorrhea is not infrequently associated with sterility. The underlying mechanism is not always clear. Although pregnancy does occur despite dysmenorrhea, which it cures frequently, the underlying factor may be part of the endocrine or other systemic disturbance which is responsible. The true explanation is not at hand and the theories advanced are for the most part speculative.

*Tests for tubal patency*. The tubal factor is one which lends itself to satisfactory evaluation because of kymographic uterotubal insufflation on the one hand and of hysterosalpingography on the other. By studying a large series of cases of sterility with both methods we are in a good position to appraise the etiologic role played by tubal obstruction. In a questionnaire which was answered by 259 gynecologists upon the results of 40,387 insufflations, tubal obstruction was found in 11,728 cases (about 28 per cent). In my own series of 3,380 cases of sterility tubal obstruction was met with in 984, an incidence of 29.1 per cent. There were an additional 16.77 per cent (567 patients) who had adherent tubes and 11.75 per cent (397 cases) who had strictured tubes. In well over half the cases there was evidence of tubal pathology which can be accorded etiological importance to preclude conception or to interfere with impregnation. I have employed radiopaque solution in a

relatively small series of cases because I have found it possible to diagnosticate all the important data relative to tubal patency or obstruction by means of uterotubal insufflation.

My first efforts in 1914, as those of William Cary, who was the first in this country to report upon intrauterine collargol injection, were directed toward x-ray visualization of the tubal lumina. I have preferred tubal insufflation with $CO_2$ gas to hysterography since 1925 when a kymograph was added to the insufflating apparatus for the following reasons: It is more convenient. Its results are immediate while, for patency to be diagnosticated by radiopaque substances, one or two days must be awaited in many instances. Uterotubal insufflation enables us within a few minutes to distinguish graphically *uterotubal spasm, tubal strictures and the physiological activity of the tubal muscle*—conditions not readily determinable by means of hysterography. Furthermore, $CO_2$ because of its prompt resorption leaves no residue in the tubes or in the pelvis, as does iodized oil, which induces foreign body granulomata, thus producing total blockage where permeable strictures had previously existed. I have observed a considerable number of women who have become totally sterile although they had the possibility of conceiving before iodized oil was injected into the uterus.

The impression is extant that by means of iodized oil one can distinguish unilateral from bilateral permeability. This is a mistake because the tube which is not visualized roentgenologically may be in a condition of spasm or it may be comparatively more hypertonic than the other tube. The hypertonic tube may also have a narrower lumen which offers greater resistance to the $CO_2$ gas. This resistance may require an increased pressure of a few millimeters of mercury in excess of that which permits the gas to be transmitted through the less spastic or more widely calibered tube. Randall has shown this to be the case with iodized oil and I have had occasion to observe the same phenomenon, i.e., on a subsequent examination an apparently closed tube became open while the open tube appeared closed.

Another advantageous claim made for hysterosalpingography is that it locates the exact point of obstruction. This can be arrived at for all practical purposes by carefully carrying out the procedure of uterotubal insufflation and paying attention to the pain reactions and distributions.

The value of x-ray opaque media in sterility lies in the fact that it enables us to demonstrate the configuration of the uterine cavity and

possibly visualize polypi and submucous myoma which may have etiological importance. But for this purpose, use of a viscous soluble crystalline iodine solution is superior as it leaves no permanent residue. Time does not permit description of the proper technique of uterotubal insufflation or of hysterography. Recently I have resumed the use of a hysteroscope which gives promise of enabling us to explore the uterine cavity in a manner quite analogous to that of cystoscopy.

*Sterility viewed from the endocrinologic standpoint.* The gross disturbances of the endocrine system are too obvious to require description here. They are moreover relatively rare. Of far greater clinical importance in relation to sterility are the less marked disturbances, the intermediary types which the French have aptly called "formes frustes." They are however not easy to define. Practically everyone knows what are the primary and secondary sex characteristics of male and female. Gross abnormalities are easily recognized whether they be in the genitalia or in the general body architecture. But there are undoubtedly some individuals, it would be difficult to say how many, who are predestined to sterility, so to speak, by failure of development and defective germ plasm.

Although we have at hand hormonal assay methods that differentiate androgenic from estrogenic hormones, these methods have not as yet enabled us to define specifically the degree of "maleness" and "femaleness" or to interpret the significance of androgen-estrogen ratios as suggested by Koch and his group. So far they have shown that both hormones are excreted by each individual; so that biologically and hormonologically, as embryologically, we are all partly male and partly female. A cyclical variation of estrogenic production and excretion has been shown for normal females in studies that have required painstaking work (R. T. Frank, et al). Carried out on a larger scale such bioassays of estrogenic and androgenic substances may lead to more reliable criteria.

At present it is useful to bear in mind certain secondary sex characters which clinical observation and anthropometric studies have established to differentiate the two sexes. Considered in relation to each other and to the whole organism they give practical aid in estimating gonadal function. These secondary sex characters are divisible into two categories, the psychic or spiritual and the somatic. On the somatic side in the female there is the finer texture of the skin and the hidden superficial

veins, the full development of the breasts and absence of body hair with longer growth of the hair of the head, the triangular arrangement of the pubic hair as opposed to the masculine escutcheon reaching the umbilicus, and the absence of beard growth. The character of the voice and speech including the recession of Adam's apple are distinctly different from that of the male. The distribution of fat about the hips and fullness and roundness of the nates, the less sturdy muscular development, the narrower skeletal development of the shoulder girdle and wider pelvic girdle, the shortness of lower extremities compared to the trunk and the swaying motion of the hips are other female sex characters. The presence of the accessory organs of the genital apparatus, namely, small clitoris, normal vagina, well developed cervix and uterus considered in conjunction with the secondary sex characters already mentioned, betoken the presence of functioning ovaries whether these are palpable or not. On the psychic side is the preference of sexual approach to men, the maternal instinct, and other generally recognized psychic characteristics of women.

If, for example, the female presents typical secondary sex characters and gives a history of normally recurring menstrual flow without pain and shows normally developed genitalia, one may, for all practical purposes, assume that her ovaries are performing their endocrine function. Since the ovaries are controlled by the pituitary, the surmise also holds for normal functioning of this motivating endocrine gland. Of all the disorders of endocrine function which have direct influence over the genital sphere, those of the thyroid are appreciable and susceptible of determination in a practical way.

It has been recognized, chiefly through the observations of Litzenberg, that a depressed thyroid state is frequently associated with sterility. The menses may be scant or they may be excessive; usually the former. There is a tendency to weight increase. The basal metabolism may show a marked reduction. Thyroid medication with dietary and physical regimens can increase fertility in these individuals.

Determination of sugar tolerance and of blood cholesterol has some clinical and endocrine significance. Blood examination and urinalysis are necessary to determine the general state of health. Hormonal assays (estrogenic, androgenic and gonadotropic) have so far yielded interesting data. Upon these data have been based corrective measures, which consisted of the administration of endocrine products but unfortunately

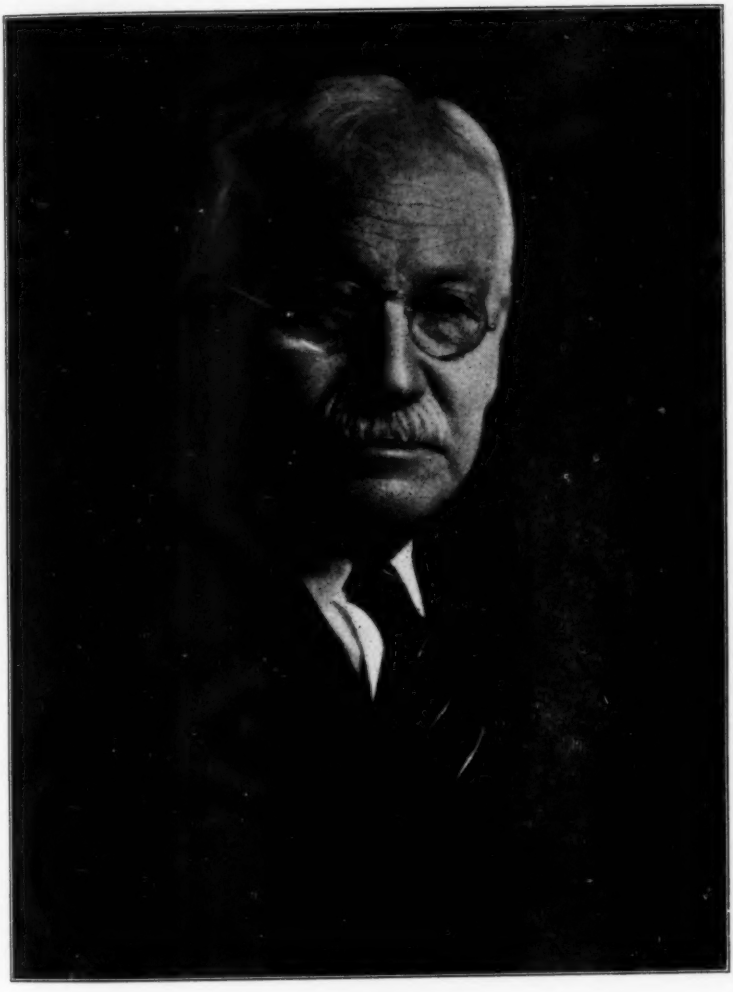
they have not proven to have the hoped for therapeutic value. At present our most reliable hormone is thyroid.

In conclusion I wish to call attention to the tendency in some quarters of overdoing the investigation of sterility. The pendulum has seemed to swing too far away from the middle of the road. From the cursory casual fashion in which sterility was managed a generation ago, there is at present a plethora of procedures many of which are not only unnecessary in every case but also are fraught with suspense and anxiety on the part of the patient which lower her susceptibility to conceive by reducing her peace of mind and general well-being.

Many examples of excessive and uncritical investigation, leading to overzealous treatment with fruitless results as a consequence, might be cited but for the limited time at my present disposal.

Obviously, those procedures should be employed that have a definite purpose supported by practical experience. In general I would emphasize the following steps in the inquiry: (1) A complete medical history especially detailed in the sphere of genital function and the constitutional state. (2) General physical examination with particular reference to that of the genitals and secondary sex characters. (3) The Huhner test and if necessary examination of the unmixed semen. (4) Tubal patency test. (5) Urinalysis; blood examination including serologic tests for syphilis. (6) BMR determination and (7) in individual cases as the indications arise, further investigation by means of specialized tests including serological, hormonological, roentgenological and biochemical.

The clinical appraisal of the patient including her psychic peculiarities, domestic happiness, dietary habits and sex habits underlying her inability to conceive must continue to receive first consideration while laboratory methods judicially applied as in other fields of medicine may serve as useful aids.



JOHN MILLER TURPIN FINNEY

1863 - 1942

# IN MEMORIAM

## JOHN MILLER TURPIN FINNEY

DR. FINNEY, John Miller Turpin Finney, professor emeritus of surgery in the Johns Hopkins University, died on May 30, 1942, at his home in Baltimore. The details of his long and distinguished career, from infancy until his retirement from active service as a surgeon, are set down in his autobiography, published in 1940. His father and, on the paternal side, his grandfather, were Presbyterian ministers, natives of Maryland, but Finney himself was born in Mississippi where his father was pastor of a church in the neighborhood of Natchez during the period of the Civil War. He had what he called a peripatetic childhood, due partly to the nature of his father's profession and partly to the fact that his mother died shortly after his birth. His school days were spent chiefly at Bel Air, Maryland, where his father had charge of the local Presbyterian church. In due course he entered Princeton University, in the sophomore class, graduating in 1884. For his medical training he went to Harvard and on completion of the course began his professional career as an intern on the resident surgical staff of the Massachusetts General Hospital. Before finishing this service he received an appointment to Dr. Halsted's staff at the newly opened Johns Hopkins Hospital in Baltimore. There he went in 1889 and there he remained for the rest of his life, in spite of flattering calls to important positions elsewhere, such as the chair of surgery at Harvard and the presidency of Princeton University. This latter call made an especially strong appeal to him for he had a deep affection for his college, and as a "Life Trustee" was directly concerned in its future development.

Some of his friends whose advice he had asked, including the present writer, felt that he ought to accept the offer with its potential possibilities of distinction and service, but after mature consideration he declined the call. He could not see himself as fitted for such a position, and, perhaps, he could not bring himself to the point of severing his ties

with surgery, the profession that he loved and in which he had been so eminently successful. Whether or not, if he had accepted the call, his own life would have been any richer or more distinguished than it actually was, no one, of course, can say. But one may feel confident that Princeton University would have profited by his acceptance. His unusually sound judgment, his tolerance and his intellectual integrity would have made him, in all probability, a safe and effective leader. Above all, it would have been of inestimable benefit to a full generation of students to have been brought into contact with his wholesome personality. One can imagine that it would have permeated and inspired the lives of many men who have since risen to positions of influence and leadership.

At this period in his life he was not only the leading practitioner of surgery in Baltimore, and distinguished in his profession, both nationally and internationally, but he had also become one of Baltimore's chief citizens, respected and loved both for his medical skill and for his services to the city and the state in connection with various educational and social institutions. When he declined the call to Princeton and decided to stay with his profession his fellow citizens and medical associates combined to give him a testimonial dinner to signify "the sense of gratitude felt by his friends at his decision to remain in Baltimore."

A similar expression of the general esteem in which he was held was a large banquet in his honor, on the occasion of his seventy-fifth birthday, at which his contributions to medicine and to the communal life were emphasized, and a personal letter from the President of the United States was read, in appreciation of his activities in the American Red Cross and of his distinguished services as Chief Consultant in Surgery to the American Army during the first World War.

Among such expressions of affection the one that probably gave him the most pleasure was a unique tribute arranged by his associate and long-time companion, Dr. George Walker. Walker came to the Hopkins from South Carolina, shortly after the opening of the Hospital, to serve on the surgical staff under Finney. He was a lovable and somewhat eccentric personality with some of the characteristics of the traditional Southern gentleman, generous, chivalrous and quick-tempered. Finney always spoke of him as Marse George. His admiration for Finney was unbounded. In Kipling's poem "If" the virtues of the ideal man are pictured in strong beautiful words:

"If you can talk with crowds and keep your virtue,
Or walk with kings, nor lose the common touch."

In Walker's opinion no one fitted this picture so well as his friend. He conceived, therefore, a plan to have Kipling sign a copy of the poem and then present it to Dr. Finney at a gathering of selected guests. Through Lord Moynihan, the English surgeon, whom he had known in France during the war, he obtained Kipling's consent to give his autograph. As promptly as possible he departed for London with a beautifully engraved copy of the poem and a special gold pen and bottle of indelible ink. His difficulties in obtaining the signature made an entertaining story which Walker's friends delighted to have him relate. Moynihan was out of the country, Kipling could not be located, their respective secretaries knew nothing of the promise and had no record of any correspondence bearing upon it. Eventually, however, he was successful, although he did not see Kipling personally. On his return to Baltimore a dinner was arranged and the presentation was made. Unfortunately Dr. Walker was not able to make the presentation himself, as was intended, since he was confined to the hospital with an illness, which subsequently caused his death, but it was an unusually pleasant and intimate occasion, for the poem did serve to express something of the high estimate that his friends placed upon the fine personal qualities of Dr. Finney, and in Walker's absence Dr. Finney seized the opportunity to pay a warm tribute to Marse George.

After the death of Dr. Halsted in 1922 Finney was asked to take the full-time chair in surgery, but declined the offer, partly because he felt that a younger man should be selected, and partly because he had some mental reservations in regard to the wisdom of a full-time professorship in surgery. He continued, therefore, as professor of clinical surgery, later professor of surgery, in the University, and visiting surgeon in the Hospital, until his retirement for age in 1933.

Until a few weeks before his death he had excellent health and was extremely active with consultations and with attendance upon the meetings of various boards of which he was a member. His major interest, perhaps, during these last years was in connection with his duties as Chairman of the Baltimore Chapter of the American Red Cross.

Dr. Finney's eminence as a surgeon is known to all members of the medical profession. One need only recall that he was offered the chair of surgery at Harvard and at the Johns Hopkins, that he received the

Bigelow Medal for Achievement in Surgery, that he was the first president of the American College of Surgeons, and that during the first World War he was appointed Chief Consultant in Surgery to the American Expeditionary Forces.

His associates and friends loved him for his own good self. He had a great heart and a remarkable gift for making and keeping friends. His professional work and his extraprofessional activities brought him into contact with all sorts and conditions of men, so that he got a close view of both the noble and the ignoble motives that control human conduct. It is to his great credit that always he emphasized the excellencies rather than the follies of his fellow-man, and his fellow-man responded by according to him a measure of confidence and affection such as few persons are privileged to enjoy.

WILLIAM H. HOWELL.

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## *DEATH OF FELLOW*

FINNEY, JOHN MILLER TURPIN: 2947 St. Paul Street, Baltimore, Maryland; born in Mississippi, June 20, 1863; died in Baltimore, Maryland, May 30, 1942; received the degree of B.A. from Princeton University in 1884; graduated in medicine from Harvard Medical School in 1889; elected an Honorary Fellow of the Academy November 18, 1926.

Dr. Finney was emeritus professor of surgery at the Johns Hopkins University and surgeon to the Johns Hopkins and Union Memorial Hospitals, Hospital for Women of Maryland, and the Church Home and Infirmary. He was one of the founders of the American College of Surgeons and its first president (1913-1916); a Fellow of the Royal College of Surgeons of Ireland, a member and former president of the American Surgical Association, and a member of the Society of Clinical Surgery.

During the World War, Dr. Finney was Chief Consultant in Surgery in the American Expeditionary Forces in France with the rank of Colonel, later receiving the rank of Brigadier General. For his war services he received the American Distinguished Service Medal; and was made Comdr. de l'Ordre de la Couroune (Belgium); Officier de la Légion d'Honneur (France).

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# *1942 GRADUATE FORTNIGHT*

## OCTOBER 12 TO 23

# "DISORDERS OF THE NERVOUS SYSTEM"

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## *The Program Includes*

MORNING PANEL DISCUSSIONS, AFTERNOON CLINICS, EVENING LECTURES, SCIENTIFIC EXHIBITS AND DEMONSTRATIONS

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## EVENING LECTURES

The subjects and speakers at the evening lectures will include:

*Pathology of head injuries* ..... Timothy Leary
*Principles of treatment of closed head injuries* ..... D. Denny-Brown
*Principles of treatment of penetrating and perforating wounds of the brain*. William Cone
*Subdural hematoma (and other late results of head injury)* ..... E. Jefferson Browder
*Military Psychiatry* ..... Edward A. Strecker
*The emotions and disease* ..... Harold G. Wolff
*Tidal drainage and cystometry in the treatment of the bladder in the presence of spinal cord injuries* ..... Donald Munro
*Diagnosis and treatment of brain abscess* ..... Joseph E. J. King
*Differential diagnosis and prognosis of brain tumors* ..... Gilbert Horrax
*Certain abnormalities of ocular movements: their importance in general and neurologic diagnosis* ..... Frank B. Walsh
*Wounds and injuries of the spinal cord* ..... Byron P. Stookey
*Surgical treatment of pain* ..... Francis C. Grant
*Treatment of speech disorders* ..... Stanley Cobb
*Multiple sclerosis and "encephalomyelitis"* ..... Tracy J. Putnam
*Limitations of vitamins in neurology* ..... Charles D. Aring
*Present status of shock therapy* ..... Nolan D. C. Lewis
*Prefrontal lobotomy* ..... Walter Freeman
*Types of psychotherapy and indications for them* ..... Lawrence S. Kubie
*Migraine and other forms of headache* ..... Henry A. Riley
*Epilepsy and its treatment* ..... William G. Lennox

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